THE LIVER OF DYSPEPTICS

BOIX

THE

LIVER OF DYSPEPTICS

AND PARTICULARLY

THE CIRRHOSIS PRODUCED BY AUTO-INTOXICATION OF GASTRO-INTESTINAL ORIGIN

(Clinical, Anatomo-Pathological, Pathogenic, and Experimental Study)

BY

DR. ÉMILE BOIX

Interne Lauréat des Hôpitaux de Paris (Médaille d'or, Concours de 1893)
Médaille d'or des Épidémies (Cholera, 1884)

AUTHORIZED TRANSLATION, FROM THE LATEST FRENCH EDITION, BY

PAUL RICHARD BROWN, M.D.

Major and Surgeon, U. S. Army

G. P. PUTNAM'S SONS

NEW YORK
27 WEST TWENTY-THIRD STREET

LONDON
24 BEDFORD STREET, STRAND

The Knickerbocker Press

1897

The Knickerbocker Press, New York

CONTENTS.

CHAPTER III.

CHAPTER IV.

CHAPTER V.

PART III.

THE LIVER OF DYSPEPTICS

THE LIVER OF DYSPEPTICS.

INTRODUCTION.

THE tendency of the human mind is to explain everything in accordance with a single principle or idea. Nowhere is this truth better exemplified than in our investigations of the causes of diseases. For many years has not cirrhosis of the liver been considered as solely due to the abuse of alcoholic drinks, as if man drank only alcohol and could not sclerose his liver by other ingesta or by substances not introduced from without but generated in the organism itself?

However, we have been compelled to consider other pathogenic agents in certain cases in which alcohol could not be implicated: lead poisoning, syphilis, impaludism, and tuberculosis have contended with alcohol for a portion of its illegitimate domain.

At present, almost without exception, we still attribute atrophic cirrhosis of the liver to the excessive use of alcoholic beverages (even taking verbatim its English name, *gin-drinker's liver*), and a hypertrophic cirrhosis, said to be curable, also bears the name of alcoholic cirrhosis. However, cases of hypertrophied and atrophied livers are daily being reported which cannot be attributed to the abuse of alcohol, as the patient did not drink it in any form, and there is now a decided reaction against considering alcohol as the only active agent in the production of cirrhosis of the liver.

It is not as a plea for the innocuousness of alcohol that I have written this work: all of my readers who are desirous of being reassured in regard to the hepatic sequelæ of the abuse of alcoholic drinks, I refer to the very interesting thesis of my colleague A. Laffitte,[1] and to a recent article of A. Létienne.[2] I only seek to establish the fact that, in addition to alcohol and entirely inde-

[1] A. Laffitte, *Contribution à l'étude de la cirrhose de Laennec*, Paris, 1892.

[2] A. Létienne, *Médecine moderne*, 1894, No. 15.

pendent of it, independent also of some hitherto recognized causes of hepatic cirrhosis, there is another which, notwithstanding its recent appearance upon the etiological scene, we have already rendered responsible for many ills, but to which we have not yet thought of attributing an active part in the production of sclerosis of the liver: I refer to auto-intoxication of gastro-intestinal origin.

There is a peculiar form of hypertrophic cirrhosis which, in the opinion of M. Hanot and myself, arises from the passage through the liver of toxic substances elaborated in a diseased alimentary canal. This is the only form which we shall here consider, but this does not imply that some other forms, even atrophic, may not have the same origin.

It is to be hoped that the future, although laden with engagements almost innumerable, as says Lasègue, will enlighten us in regard to this important question. The *dyspeptic liver* will perhaps never have the undeserved renown of the *alcoholic liver*, and this will be all the better for its reputation. In the etiology of the cirrhoses, we must put in its proper place every pathogenic agent, whatever it may be, and only accord efficacious action to it when the circumstances prepare and favor this injurious action. We cannot become cirrhotic at will, even by drinking to excess, even by taking toxic substances as ingesta, or by bringing on a gastritis which permits abnormal fermentations in the alimentary canal: if we have not inherited the secret influence which produces the gouty diathesis, the intentional alcoholic or dyspeptic only stands a very great chance of altering his hepatic cells.

The gouty diathesis is the domain par excellence of the scleroses, and predisposition is as indispensable to the greater part of the chronic processes, as receptivity is essential in order to contract the majority of infectious diseases. Here vanishes the dream of those who are wedded to a single cause, and who would like to reduce to a simple equation the relation of a poison or a microbe to a given disease.

At the present time, these ideas may appear hackneyed, yet whenever pathogeny is in question, especially if we are considering some new cause, we permit ourselves to attribute to it, without regard to the surrounding conditions, the disease in its totality and even connect other affections with it. I should like to escape this reproach and not appear to see in dyspepsia a source of evils for which it is not responsible.

I employ the word dyspepsia in its broadest signification, here including every defective functioning of the alimentary canal, whatever may be its cause, and it is for the sake of abbreviation, so to speak, that I term the sclerosis of the liver which results from an auto-intoxication of gastro-intestinal origin, *dyspeptic cirrhosis*. It is especially in order to place this form of cirrhosis in opposition to alcoholic cirrhosis. The term *toxic cirrhosis* would have been too comprehensive, as the toxic cirrhoses are numerous, here including alcoholic cirrhosis. I desire then that the terms *dyspeptic liver* and *dyspeptic cirrhosis* be only considered as a handy means of expression and also as a means of abbreviation.

Prior to our taking up the study of the clinical forms, which is the subject of the principal portion or this work, it is essential that a sort of general picture should be presented of the pathogenic elements concerned. To this I have devoted the first part, which includes three chapters; one treating of auto-intoxication of gastro-intestinal origin, another enumerating the products of fermentation capable of exercising a pathogenic action, and last of all, a glance at the conditions which favor abnormal fermentations and the production of these poisons.

In a second part, after some preliminary considerations in regard to the anti-toxic rôle of the liver, comes the history of the dyspeptic liver with its two forms, congestion and cirrhosis. Next I consider the anatomical form of dyspeptic cirrhosis and its place among the scleroses of the liver.

The third part is devoted to the relation of my personal experiments with some of the agents *à priori* suspected as causes of gastro-intestinal fermentations, and the successful results of which will show, as I hope, the legitimate influence which the dyspepsias may claim in the etiology of the cirrhoses of the liver.

PART I.

Auto-Intoxication of Gastro-Intestinal Origin.

CHAPTER I.

GENERAL CONSIDERATIONS.

"In the normal as well as in the pathological condition, the organism is a receptacle and laboratory of poisons" (Bouchard[1]). With a precision which is almost mathematical, the learned work of the eminent professor develops this fatal aphorism; the secret of the disturbances of the organism, and also perhaps the secret of their relief.

Toxicology is becoming, as it were, almost the whole science of medicine, as it is extending its domain beyond the mineral and vegetable world; and it is to be hoped that it will inform us in regard to the various microbian poisons and their effects, and will also demonstrate to us how we may be able, by opposing other poisons to these poisons, to neutralize or weaken their action; for every medicine is a poison and every poison a medicine.

Owing to the powerful impulse given to it by M. Bouchard, the doctrine of auto-intoxication is now dominant in pathology, with the exception of such diseases as arise from exogenous intoxications and from specific infections; and even these are frequently seconded by auto-intoxication. This term is difficult to define, not that we do not understand its signification, but because we cannot exactly state its precise limits.

Must we only accept the word in its literal sense and solely connect with it the poisons fabricated in our organism and by its cells alone? Or shall we consider as autochthonous poisons all those which originate within us, whether they proceed from our elementary organs (organites) or from their habitual guests, the micro-organisms? The latter interpretation, both broader and

[1] Bouchard, *Leçons sur les auto-intoxications dans les maladies*, Paris, 1887.

truer, appears to be in accordance with the majority of pathological processes, as frequently it is impossible to give to each of these poisons of different origin its due share in the production of disease. This is the generally received opinion and is also that of M. Bouchard, who explains it very clearly.

Now, in what part of the human organism can these poisons be found in greater quantity than in the alimentary canal, especially when there is any interference with its normal functions? "We have certainly accepted the fact, not without some difficulty however," says M. Bouchard,[1] "that certain general accidents may result from disease of the kidneys, and I am of the opinion that the functional dignity of these organs is less than that of the alimentary canal; they excrete matter without modifying it, and yet how many disturbances their diseases produce in the organism?

"What may not take place when the stomach is diseased, the functional derangement of which throws the whole intestine into disorder? Why does not its derangement react upon the whole organism? Think of the physiological importance of the alimentary canal; it introduces every substance solid and liquid into the body, save oxygen, and before introducing matter, it must elaborate it. It does not then play simply an excretive rôle: its improper functioning must affect certain emunctory apparatuses and the cells of the whole organism."

This idea is certainly not a modern one, since it dates back to the time of Hippocrates,[2] who was of the opinion that the stomach bears the same relation to animals as the soil does to plants: *ut in arboribus terra, sic in animalibus alvus succum alibilem suppeditat.* From whence it follows, says Beau, that the man, whose digestion is defective, is comparable to a tree which, planted in sterile soil, finishes by withering and perishing. *Morborum fere omnium causa est stomachi infirmitas*, also says Benedetti.[3] We know, moreover, the excessive importance which Broussais attached to gastro-enteritis, and it is almost Broussism which is springing up to-day in another form.

Beau[4] more than merely calls attention to the fact that deleterious products may be elaborated by a diseased stomach, for he

[1] Bouchard, *loc. cit.*, p. 181.

[2] Hippocrates, *De humoribus*, cap. iv.

[3] Alexander Benedictus, *Opera*, p. 1125, Basileæ, 1539.

[4] Beau, *Traité de la dyspepsie*, Paris, 1866, p. 37.

says: "When these symptoms occur during the act of digestion, we may always ask ourselves if they depend upon a purely sympathetic irritation or possibly upon an irritant digestive product carried to a greater or less distance from the stomach by the circulation.

"To a great extent certain of these symptoms are connected with the alteration of the blood which follows the dyspeptic condition." The systematic investigation made by Beau in regard to these alterations of the blood illy accords with late discoveries; but his doctrine of a *chylopathy* causing the *hemopathic series* of dyspeptic disturbances is not displeasing to modern humoralism.

The list of accidents and symptoms is long, which modern writers attribute to auto-intoxication of gastro-intestinal origin, and the theory of Beau in regard to the diseases which are connected with dyspepsia does not now appear so ridiculous. M. Bouchard derives from it "accidents so varied and multiple, that their enumeration at first sight provokes our incredulity." Besides those affecting the alimentary canal and the liver, in regard to which farther on we will find more details, there is a whole series of accidents remote from the dyspepsias; those which we have hitherto considered as reflexes and which really are of toxic origin.

Nervous Accidents.—Exhaustion on awakening, headache, sadness, irritability, sensitiveness to cold, sleeplessness, vertigo, disturbances of vision, hallucinations, partial, and temporary numbness of the limbs, contraction of the extremities, transient aphasia, fainting, palpitation of the heart, pseudo angina pectoris, night sweats, intercostal neuralgia.

Cutaneous Accidents.—Alteration of the secretion of the sudoriparous and sebaceous glands, eruptions such as eczema, pityriasis versicolor, urticaria, acne.

Renal Accidents.—Albuminuria, peptonuria.

Accidents Affecting the General Nutrition.—Loss of strength, lessening of physical and mental vigor, emaciation, etc.; the osseous system itself is not spared, and manifests its suffering by enlargement of the base of the second phalanx (nodosities of Bouchard), and sometimes by osteomalacia.

According to M. Comby,[1] dyspepsia, in its broadest sense, is the cause of rickets (dissolving action of the acids of fermentation: lactic, acetic, etc.). A pupil of these two physicians[2] has

[1] Comby, *Traité du rachitisme*, Paris, 1892.

[2] René Millon, *Thèse de Paris*, 1893.

written a thesis in regard to the cutaneous manifestations due to improper nutrition in children, in which digestive disturbances take a prominent part in the etiology.

Lastly, according to M. Bouchard, several diseases are occasionally due to the gastropathies: chlorosis, pulmonary phthisis, typhoid fever.[1] For M. Bazy,[2] gastrectasia would play, in the genesis of the complications of wounds, accidental or surgical, a rôle analogous to that of alcoholism, impaludism, diabetes, etc. In the gastric disease called "permanent hypersecretion or Reichmann's disease," Bouveret and Devic[3] have studied the pathogenesis of tetany, already well known through the labors of Neumann, Kussmaul, Galliard, Laprévotte, Dujardin-Beaumetz, etc.

From the products of digestion collected for a month, they have succeeded in preparing an alcoholic extract producing a marked convulsive action upon animals; they also attribute tetany to intoxication of gastric origin. Debove and Rémond[4] have not been able to verify the assertions of Bouveret and Devic. But very recently, E. Cassaet and G. Ferré (of Bordeaux)[5], investigating from this point of view the gastric juice of a hyperpeptic, who never had manifested any symptoms of tetany, have been able to provoke, with the rabbit, in numerous experiments, very violent convulsive phenomena: they add that the substance extracted from hyperchlorhydric stomachs is, besides, vaso-constrictor, myositic, anæsthetic, and immediately dyspnœic.

Brieger[6] had previously isolated, in the products of the digestion of albuminoid matters, a substance likewise convulsive, pepto-toxin, corresponding chemically to the bodies of the series $C_nH_{2N+1}NO_2$. The tetanizing poison of Bouveret and Devic is different from this pepto-toxin. These authors also attribute to it the *gastric epilepsy*, the so-called *congestive epilepsy*, observed by Pommay,[7] especially with plethoric people and great eaters, as the result of errors of diet, of large meals, and of the abuse of alcoholic drinks. The latest utterance in regard to poisoning by the toxic substances of the intestinal tract is the comatose

[1] P. Le Gendre, *Dilatation de l'estomac et fièvre typhoïde*, Paris, 1886.

[2] Bazy, *Arch. gén. de médecine*, mars, 1889.

[3] Bouveret et Devic, *Revue de médecine*, janvier et février, 1892.

[4] Debove et Rémond, *Traité des maladies de l'estomac*, p. 366, Paris, 1894.

[5] Cassaet et Ferré, *Soc. de biologie*, 23 juin, 1894.

[6] Brieger, *Microbes, ptomaines et maladies*, Paris, 1887.

[7] Pommay, *Revue de médecine*, 1881, p. 449.

condition observed by von Jaksch, who compares it to diabetic coma.

Litten [1] has noticed it in grave dyspeptic conditions, and has described it under the name of *dyspeptic coma*. Stadelmann,[2] Minkowski,[3] Lépine,[4] attribute it to an acid dyscrasia, of which one of the principal factors is probably oxybutyric acid. Now, in the urine of patients affected with cancer of the stomach, Klemperer [5] has found this acid, von Jaksch some acetic acid, and Senator a marked quantity of indican, which results from the putrefaction of albuminoids in the stomach and intestines. By the side of dyspeptic coma we should place that which Humbert has called *intestinal septicæmia*.

Here then is a true Iliad of evils chargeable to auto-intoxication of gastro-intestinal origin. As far as the conditions of our chemical and bacteriological knowledge will permit, we should now study the normal and abnormal products of the alimentary canal, as well as the factors of these products, the microzoa, guests of the mouth, the stomach, and the intestines. But in order to take into consideration all the poisons which may be encountered in the digestive system, it is essential to enumerate those which, under a disguised form, are introduced in our food; their rôle is not unimportant, whether they act by themselves or whether they produce a disturbance of the digestion capable of giving rise to other toxic substances.

[1] Litten, *Berliner klin. Wochenschr.*, 1882.
[2] Stadelmann, *Arch. f. exp. Pathol.*, Bd. xvii., p. 419.
[3] Minkowski, *Berlin. klin. Woch.*, 1887.
[4] Lépine, *Revue de médecine*, mars, 1887.
[5] Klemperer, *Berlin. klin. Woch.*, 1889.

CHAPTER II.

THE POISONS OF THE ALIMENTARY CANAL.

Poisons of Alimentary Origin.—The history of botulism, which commences in 1735, in connection with poisoning by sausages, is now too well known for it to be necessary for me to dwell upon it. The researches of Hoppe-Seyler, Brouardel, and Boutmy, Gaspard and Panum, Bouchard, Selmi, Gautier, etc., have shown that the accidents due to the ingestion of spoiled pork, pickled goose, and decomposed meats in general are caused by very toxic alkaloids.

Fish, lobsters, oysters, snails, mouldy bread, cheese, and putrid water also frequently contain analogous poisons. A list of them may be found in the work of M. Charrin: "Poisons of the Organism."[1] Microbes are not lacking in the ingesta. Speaking only of bread, it may contain, even when in a good condition of preservation, the *Penicillium glaucum*, the *Ascophora nigricans*, the *Oidium aurantiacum*, and the *Mucor mucedo.*

As to water, even potable, I will not undertake an enumeration of the micro-organisms which may be present in it: however we must not forget the typhoid bacillus and the *Bacterium coli.* There are in bread, especially in the soft part, some substances which farther on we shall see are injurious, if they are present in sufficient quantity. Bread fermentation affects two elements: starch and gluten. Starch, in presence of diastase, is split up into maltose and dextrin.

Maltose, under the influence of *Saccharomyces minor*, furnishes two sugars, dextrose and levulose, which ferment in their turn in order to produce *alcohol* and *carbonic acid* (Graham). Gluten, in the presence of the *Bacillus glutinis*, during the baking of bread, gives off some acetic, butyric, and lactic acids. We also find in bread some leucin, tyrosin, and phenol—that is, the products of the fermentation of a nitrogenous substance (Chicaudart). Even in the centre of the loaf, the Bacillus glutinis resists the elevated

[1] Charrin, *Encyclopédie Léauté*, Masson, Paris, 1893.

temperature of the oven and may continue the acetic fermentation in the stomach (Bouchard).[1]

"With certain persons," says M. Bouchard, "some particular foods, without being in any respect toxic or putrid, invariably cause indigestion and various grave phenomena. In such a case, if there is poisoning, it is the fault not of the food, but of the non-digestion; the gastric juice will not transform a food which the stomach does not care to receive; the nervous system produces secretory disturbance and the gastric juice ceases to flow into the stomach, or possibly hydrochloric acid is absent from it at the moment of the conflict of the food with the microbes. Abnormal fermentations take place in the stomach and intestine; the toxic products of these fermentations are absorbed; thence poisoning results."

This is not a simple hypothesis, since, in a case of this kind, M. Bouchard has been able to ascertain the quantity of the microbes present in a third of the fæces, which contained fifteen milligrams of alkaloids per kilogram. There was also found in the urine an amount of alkaloids fifty times above the normal, and this through the multiplication alone of the normal bacteria of the alimentary canal.

Poisons Fabricated in the Alimentary Canal.—It is now positively established that, as Prout claimed in 1824,[2] and as Richet and Berthelot have especially proven, the normal acid of the gastric juice is a mineral acid, hydrochloric acid. Let this acid be set free secondarily in the stomach, by means of its secretion of alkaline chlorides, as Hayem and Winter have claimed, or that, as Ewald,[3] Martins, and Lüttke have shown,[4] it results directly from glandular functioning (parietal cells of Heidenhain or delo-

[1] Very recently Walsh (British Medical Association, session of 1894) has proven that bread, fresh from the oven, is not sterile, and that a goodly number of microorganisms, and especially spores, situated in the centre of the loaf, resist the high temperature of the oven. He propounds the question, whether bread in such a case would not be an excellent medium for the propagation of disease and, especially, of gastro-intestinal affections.

George Brown is of the same opinion, and, in certain choleriform affections, of which he has endeavored to ascertain the cause, he has been led to incriminate the bread ingested, and has finally discovered that the flour employed in its manufacture was damaged.

[2] Prout, *Phil. Trans.*, 1824.

[3] Ewald, *Zeitschrift f. klin. Med.*, 1892.

[4] Martins and Lüttke, *Die Magensaure des Menschen*. Stuttgart, 1892.

morphous cells of Rollet),[1] makes but little difference; all that is necessary for us to remember is that normally there is in the stomach no other acid than hydrochloric; or rather that this alone is necessary for digestion. Whence it follows that the organic acids which may there be encountered are at least useless if not injurious. But before saying anything in regard to them, it will be well to consider the variations of the hydrochloric acid of the stomach, it having been considered as an antiseptic opposing itself to the production of organic acids and abnormal fermentations. In fact, this is what the experiments *in vitro* of Cohn and Hirschfeld,[2] Strauss and Wurtz, have appeared to demonstrate.

If the gastric juice of the dog or of man, which contains in the normal state an infinite number of microbes, is infected inside of twenty-four hours after its extraction, in a few days the colonies there developed are *innumerable;* with gastric juice four days old, they are still present in considerable number (675 in an Esmarch tube); their development is only completely prevented with gastric juice eight days old.

A certain time, shorter or longer, is then necessary to enable the gastric juice to destroy the microbes and the germs which it contains. Hydrochloric acid diluted with water in the same proportion in which it is found in the various gastric juices, comports itself, from this point of view, almost exactly the same as the gastric juice itself. But what shall we think in regard to the anti-fermentative action of a gastric juice diluted by foods and drinks, especially at a time when the microbes are more or less inclosed in animal and vegetable tissues and in part protected by them?

Also both MM. Strauss and Wurtz acknowledge that in their experiments "the antiseptic effect obtained is a *maximum* effect which is never realized in physiological digestion in the same proportions." According to Miller, there are at least two parts per thousand of HCl necessary in order to arrest the fermentations produced by the microbes which he has found in the digestive passages. We are then obliged to consider the antiseptic rôle of hydrochloric acid as comparatively unimportant, and we have not the right to conclude on the greater or less probability of abnormal fermentations in a stomach, according to the quantity of hydro-

[1] Swiccicki and de Sehrwald, *Munch. med. Wochenschrift*, No. 11, 1889.

[2] Strauss et Wurtz, *Arch de méd. expérimen.*, 1889, p. 370.

chloric acid which it contains. Experiments likewise have well demonstrated this fact.

Lesage,[1] comparatively examining the micro-organisms of a certain number of stomachs variously affected, has arrived at this conclusion, apparently paradoxical; that there are few microbes in *hypo-chlorhydric* stomachs, and that there is a much greater number of them in *hyper-chlorhydric* stomachs. Now, these are the microbes which produce fermentations. Bouveret[2] a long time previously had noticed that microbes were present in liquids removed from stomachs affected with permanent hypersecretion, and Mathieu and Rémond[3] had ascertained that, in the dilated stomachs of individuals secreting hydrochloric acid in excess, the organic acids of fermentation attain a figure as high as in cancerous stomachs devoid of hydrochloric acid. Soupault[4] has frequently observed the same thing. *Fermentations are then frequent in all the varieties of gastric chemism.*

It was important to establish this fact in the first place.

Lactic Acid.—We have above seen that a certain quantity of lactic acid is borne into the stomach by the crumb of bread; there is also a considerable proportion of it (sarco-lactic acid) in the lean meat taken as food. Lastly, it proceeds from the buccal fermentation of amylaceous foods under the influence of the ptyalin contained in the saliva, and of the *Bacillus lactique* of Pasteur (or of a bacillus very similar and endowed with the same property), which Miller[5] has found in the mouth.

Besides, a certain number of microbes introduced into mediums containing carbo-hydrates there develop a fermentation of which one of the products is lactic acid. The lactic fermentation transforms milk sugar into lactic acid, the milk sugar passing in the first place probably into the state of glucose of which two molecules give four of lactic acid.

$$2(C_6H_{12}O_6) = 4(C_3H_6O_3).$$

This acid is found in the stomach and is there found alone at the commencement of digestion. In proportion as HCl is secreted,

[1] Lesage, *cité par* Hayem, *Leçons de thérapeutique*, 4 série, p. 201.
[2] Bouveret, *Traité des maladies de l'estomac*, 1893, p. 132.
[3] Mathieu et Rémond, *Soc. méd. des hôpitaux*, 1892.
[4] Soupault, "Des dyspepsies nerveuses," *Thèse de Paris*, 1893, p. 35.
[5] Miller, *Die Microorganismen der Mundhole*, Leipzig, 1889.

the lactic acid diminishes and finally completely disappears. This fact has been demonstrated by Ewald and Boas,[1] who distinguish three periods in the digestion of a mixed meal:

Pure lactic acid stage.....50 to 60 minutes.
Lacto-hydrochloric acid stage.....60 to 70 minutes.
Pure hydrochloric acid stage.....Until the end.

After the test meal of Ewald, it is seldom that the proportion of lactic acid encountered with a healthy man exceeds 0.1 to 0.3 p. 1000; there is generally no decided reaction with Uffelmann's solution; a quantity sufficient to produce the characteristic yellow coloration is an indication of a pathological condition and, say Debove and Rémond, very frequently of cancer of the stomach.

Lactic acid, even in the form of lactate of soda, is toxic. Klein,[2] a pupil of Lépine, with the guinea-pig, has been able to produce death with a dose of about a gram and a half per kilogram of weight. MM. Bourget and Frémont[3] think that by itself alone lactic acid may produce pyrosis. We shall see further on how it affects the liver.

Acetic Acid.—In this respect it is the same with acetic acid. This acid (or its ethers), the odor of which is easily recognizable, is present in large quantity in matters vomited during indigestion; we encounter it in the stomach of alcoholics and dyspeptics.

It is owing to the *Mycoderma aceti* that the alcohol is transformed into acetic acid.

$$C_2H_6O + {}_2O = H_2O + C_2H_4O_2.$$

This transformation cannot take place in the stomach, as it ceases at 35° C. But acetic acid is an accessory product of the lactic fermentation of carbo-hydrates, and consequently we always find it associated with lactic acid in the vomited matters of infants at the breast.

Bouveret[4] has remarked that the acetic fermentation rather accompanies the dilatations with hypersecretion, whilst the butyric fermentation is usually encountered in cases of diminution of the secretion of hydrochloric acid. This observation, he says, coincides with the results of the experiments of M. Paschutin, which demonstrate that HCl arrests the butyric fermentation.

[1] Ewald and Boas, *Virchow's Archiv*, Bd. C et CI.
[2] Klein, " De la fatigue et du surmenage," *Th. de Lyons*, 1886.
[3] Bourget et Frémont, *cités par* Soupault, *loc. cit.*, p. 48.
[4] Bouveret, *loc. cit.*, p. 125.

Butyric Acid.—The sharp and nauseous odor of this acid is particularly well known to dyspeptics. This odor is so penetrating that in the open air a drop of it can be smelled at some distance and for several hours.

It is synonymous of abnormal fermentation; its presence in the digestive liquids, especially in appreciable quantity, is in some sort pathognomonic. The agents of the butyric fermentation are numerous; we know the principal ones: the *Bacillus butyricus* of Pasteur or *Clostridium butyricum* of Prazmowski, the *Bacillus amylobacter* of Trécul and Van Tieghem, the *Bacillus butylicus* of Fitz. All these organisms are anaërobic; their action is also favored by the presence of the *Bacillus lacticus* which absorbs oxygen.

In fact, the lactic fermentation precedes the butyric and it is upon the lactic acid that the anaërobic bacilli act, giving off butyric acid, carbonic acid gas, and hydrogen:

$$2(C_3H_6O_3) = C_4H_8O_2 + 2CO_2 + 4H.$$

The hydrogen which we find in dilated stomachs proceeds from this reaction. O. Weber has noticed that cats are very sensitive to the action of butyric acid and Meyer[1] has confirmed this observation.

Valeric or *Valerianic Acid.*—This acid has been only rarely observed in gastric liquids; undoubtedly because we seldom seek for it. It is likewise quite difficult to distinguish from butyric acid, to the series of which it belongs. It is a product of the oxidation of amylic alcohol, which drunkards frequently ingest in large quantity. Leucin, a product of the putrefaction of albuminoid matters, also easily gives rise to valeric acid, especially in an alkaline medium, as it is a residue of defective digestion.

Propionic Acid.—This acid has sometimes been found in the gastric juice and particularly in that removed from the stomachs of individuals suffering from dilatation (Debove and Rémond). We never look for it in the ordinary examination of the contents of the stomach. It is the homologue immediately superior of acetic acid. In an alkaline medium it arises in the oxidation of sugar, starch, gum, alcohol, and acetone. Meyer has observed that the propionate of soda, in the dose of a gram to the kilogram of weight, produces great somnolence with the cat.

[1] Meyer, "Recherches sur l'action toxique de quelques *acides* de la série grasse," *Arch. f. exp. Pathol.*, Bd. xviii.

Fatty Acids.—Oleic, palmitic, margaric, and stearic acids are ingested with all the fats. They are found in great quantity in the alimentary canal where saponification takes place. But they may be set free in stomachs the seat of putrefaction. They only appear to have, from a toxic or irritant point of view, a very slight importance, as we shall see in the experimental portion of this work; but their presence in the stomach contributes to promote the abnormal fermentations.

Oxalic Acid.—This, certainly, is a poison. It exists in the organism in the state of oxalate of calcium, and passes unperceived during a condition of health, as it is destroyed in the blood, where it passes into the condition of urate, and is eliminated by the urine. Its origin is easily explained, not only by the ingestion of foods which contain it (sorrel, tomatoes, rhubarb), but in addition because it is one of the most common products of the oxidation of organic substances. In fact, the oxidations, in the organism as well as in the alimentary canal, are made the most of and it is only gradually and through intermediate substances that we arrive at the last terms of the oxidation of a body.

It is thus that uric acid, through incomplete oxidation, gives rise to it instead of being reduced into urea and carbonic acid. A *retardation of nutrition*, an incomplete hematosis, favor the production of oxalic acid; under these circumstances the inosite of the muscles and the glycogen of the liver are its principal sources. In the alimentary canal its presence and its formation have hitherto been but little investigated.

We however understand that it may result from the incomplete oxidation of starches and sugars, as well as from reduction of carbonic anhydride after the ingestion of beverages which contain it (sparkling wines, beers, etc)., or from acid carbonates. It is also one of the derivatives of leucin. Bayard[1] has considered it as the product of certain gastric affections. Very recently, Dr. Boursier[2] (of Contrexéville, old interne of the Paris hospitals), has expressed the same opinion.

"With certain patients," he says, "oxalate of lime appears to be constantly eliminated and to be accompanied by certain symptoms (dyspepsia, nervous disturbances), which seem to give rise to a special disease: *oxaluria.* But *dyspepsia* is one of the

[1] Bayard, *Traité pratique des maladies de l' estomac*, 1872, page 213.

[2] A. Boursier, *Ann. de la Soc. d' hydrologie*, analysé en *Journal de méd. et de chir. pratiques*, 25 juin, 1884.

most frequent of symptoms with oxalurics, and the formation of oxalates would seem to be a consequence of this dyspepsia. *Oxaluria would be rather a symptom of a form of dyspepsia than a distinct disease.*"

That which well shows that there is here an auto-intoxication, a chemical impregnation, is that there are in these cases headaches, disturbances of vision, as in uræmia; the skin is dry and rough, is sometimes covered with profuse sweats; boils and carbuncles are frequent.

Aldehydes.—The aldehydes are the first products of the oxidation of the alcohols; but it is not solely as derivatives of the alcohols that they here have their place.

"In a celebrated hypothesis, Liebig has admitted that the organic acids once formed may give rise to aldehydes by a further reduction" (Wurtz, *Chimie biologique*). On the other hand, Guckelberger,[1] by oxidizing albuminoid matters, has obtained notable proportions of ordinary, propionic, butyric, and benzoic aldehyde (essence of bitter almonds). Now, the organic acids are formed in dilated stomachs, and the albuminoids there undergo every species of transformation. Supposing that the aldehydes of themselves have no injurious influence (see the experimental portion), they obtain one by the property which they have of producing an acid under the influence of the agents that oxidize ordinary alcohol:

C_2H_6O	C_2H_4O	$C_2H_4O_2$
Ethylic alcohol.	Ordinary aldehyde.	Acetic acid.

Through its agency we again find acetic acid. In fact, the presence of a small quantity of aldehyde has been observed in vinegar (Œchsner de Coninck). In alcoholic fermentations protected from the air, the alcohol is oxidized into the state of aldehyde (Schutzenberger and Destrem); the fungus of muguet transforms alcohol into aldehyde (Linossier and G. Roux); lastly, the simple exposure of aldehyde to the air is sufficient to transform it into acetic acid.

Acetones.—The acetones are the aldehydes of the secondary alcohols. We know that, since Markownikoff has observed their presence in the urine of diabetics, to acetone is attributable the principal rôle in diabetic coma. Stadelmann, Kulz, Minkowski,

[1] Guckelberger, *cité par* Œchsner de Coninck, *Chimie organique*, 1892.

and Lépine[1] have shown that acetone is only the last term of the oxidation of β oxybutyric and diacetic acids, and that it is to this acid dyscrasia that it is proper to attribute the diabetic coma.

In fact, β oxybutyric acid is a superior homologue of lactic acid, and on this account is probably more toxic. Now, whence come these acids? They arise from the fermentation and chemical splitting up of albuminoid matters under the influence of gradual oxidations: the acetone is only the *evidence* of these complex processes leading to the formation of intermediate toxic products. These imperfect transformations of the albuminoids do not take place solely in the inmost recesses of our tissues, as in diabetes, but also in the alimentary canal.

H. Lorenz,[2] assistant of Professor Nothnagel, has carefully studied the *acetonuria and diaceturia of digestive origin.* As early as 1860, Kaulich had found acetonuria in various diseases which had digestive disturbances as a common symptom, and had recognized the fact that acetone was formed in the gastro-intestinal tract. Von Jaksch[3] has again found it in a goodly number of pathological conditions, particularly in *dyspeptic coma.* Lorenz has very carefully investigated this subject; he has encountered acetonuria, and sometimes diaceturia, in digestive disturbances consecutive to the ingestion of spoiled meats; in ulcer and dilatation of the stomach, in chronic gastro-enteritis, but more especially in acute cases.

The aggravation of the symptoms coincides with an increase of the acetone eliminated. He has again found acetone, but with less constancy, in the neuroses of the stomach, the gastric crises of tabes; in four cases of hysteria with digestive troubles there was acetone in the urine; in two of them, some acetylacetic acid; in one, some β oxybutyric acid. Lorenz regards as arising from the intoxication produced by acetone, or by other substances intermediate between the albuminoids and this body, certain symptoms which are ordinarily connected with digestive disturbances; such as a sensitiveness of the epigastrium and spontaneous pains (cramps) in the region of the stomach.

He believes that these phenomena arise from an irritation of the cœliac plexus, the extirpation of which would determine acetonuria, according to Churton and Lustig.

[1] Lépine, *loc. cit.*

[2] Lorenz, *Zeitschr. f. klin. Med.*, xix. Bd.

[3] Von Jaksch, *Zeitschr. f. klin. Med.*, xi. Bd.

On the other hand, functional disturbances of the cœliac plexus lead to abnormal fermentations, and may also produce acetonuria. Lorenz considers the alimentary canal as the place of production of acetone in cases of digestive acetonuria. He has found this substance in matters from the stomach and, especially from the intestine, in all his clinical cases, save in the nervous affections of the stomach.

Other Poisons.—We besides observe in the stomach the presence of *syntonin* or acid albumen which, if it is not ulteriorly transformed into peptones, would have a certain toxicity. All these first terms of the digestion of albuminoids are yet imperfectly known, especially from the stand-point of their noxiousness.

Let us not forget the *peptotoxin* of Brieger. Lastly, if we pass to the intestine, besides the bodies already mentioned, we will find the *excretory products of the bile*, very toxic of themselves (since 5 cubic centimetres of ox bile kills a rabbit weighing 1500 grams), and which, in part, are absorbed by the intestine: *indol*, *scatol*, *cresol*, the *phenols*, the *excretin* of Marcet, the *salts of potash*, *carburetted* and *sulphuretted hydrogen*, etc.

M. Bouchard has shown in an exact manner the toxicity of the intestinal contents. An aqueous and especially an alcoholic extract of fæcal matters in small amounts kills various animals.

Micro-organisms.—The various products above enumerated result, for the most part, from the action of micro-organisms, ferments or microbes, contained in the alimentary canal. They are swallowed with the food, either originally contained in it or mixed with it in its passage through the mouth: a large number are carried into the stomach with the swallowed saliva. Lastly, certain species normally inhabit the stomach and especially the intestine, in which the permanent alkalinity of the medium favors their multiplication. To-day we no longer speak of the antifermentative property of the bile. Létienne[1] has shown that its antiseptic action is much less than has been commonly supposed. Certain microbes, such as the *Staphylococcus aureus* and the *Bacillus coli communis*, easily live in pure bile. Certain biles are also particularly propitious to the development of organisms.

In even the normal stomach, bacteriologists have discovered the presence of numerous species. The *sarcina*, discovered in 1842 by Goodsir, and since that time thoroughly investigated by

[1] Létienne, *Thèse de Paris*, 1891.

Falkensheim, has no peculiar signification. It is especially plentiful in dilated and cancerous stomachs. Some cases have been cited, says Bouveret, in which a drop of gastric liquid was as rich in sarcinæ as a drop of culture liquid.

De Bary has found several fungi: the *Oïdium albicans*, the *Leptothrix buccalis*, and a new one which he calls *Bacillus geniculatus*. Abelous[1] has counted in the healthy stomach sixteen species of which seven are known: the *sarcina*, *Bacillus pyocyaneus*, *Bacillus lactis erythrogenes*, *Bacillus subtilis*, the *Vibrio rugula*, *Bacillus amylobaeter*, *Bacillus megaterium*. Capitan and Moreau[2] have isolated three undetermined types. In addition, there are some yeasts, among which the *alcoholic yeast*. Lastly, we have incidentally observed the microbes of various fermentations.

But, in diseased stomachs with lessened secretion, the *Bacillus coli communis* is, according to Lesage, the most frequent; its virulence is insignificant. However, two Italian experimenters, MM. Cesaris-Demel and Orlandi,[3] have been able to convince themselves that the *Bacillus coli* acquires great virulence by its culture in gastric juice, to such an extent that guinea-pigs, ordinarily little sensitive to the action of this microbe, succumb consequent upon an injection of a cubic centimetre of this liquid into the peritoneum.

The *Bacillus coli* is an especially dangerous guest to the intestine; it reigns there despotically; it there freely multiplies and it borrows, from some conditions which we as yet very imperfectly understand, an exaltation of its virulence more or less temporary which may elevate it to the rank of a pathogenic microbe. Its secretory products, even when it appears the most inoffensive, must always be looked upon with suspicion.

The list of pathological acts which they attribute to it daily grows longer, and its history becomes more complex and as sombre as that of many a nobler microbe whose toxicity is fixed and determined. It is a hardy species which accommodates itself as well to the presence as to the absence of oxygen and gains fresh strength by its association with other microbes; it is the parasite *par excellence*, as well of man as of the lower animals and of the other micro-organisms themselves, and well knows

[1] Abelous, *Thèse de Montpellier*, 1888.

[2] Capitan et Moreau, *Soc. de biologie*, 1889.

[3] Cesaris-Demel et Orlandi, *Acad. méd. de Turin*, séance du 28 janvier, 1893.

how to turn to its own advantage every opportunity of injuring its host. For its natural habits and pathological rôle, be kind enough to refer to the excellent monograph of Macaigne,[1] and to the various articles since published in the transactions of the biological and hospital societies by different authors, among others, by my preceptor, M. Hanot,[2] and by myself.[3]

Although they have their importance, not only as agents of distension, but also as mediums destitute of oxygen and therefore favorable to the growth of the majority of microbes, I shall say nothing in regard to the *gases of fermentation:* carbonic acid, hydrogen, and sulphuretted hydrogen. In the diseased stomachs of alcoholics and of those individuals suffering from dilatation we frequently find *bile* and *pancreatic juice*, the reflux of which is rendered easier by the atony of the pylorus and by the existence of a duodenal alteration.

Their alkalinity greatly favors the secondary fermentations and the production of organic acids; the bile, moreover, contains the excrementitious matters of the liver, and the pancreatic juice a certain quantity of fatty acids. We have just read something in regard to the present opinion in reference to the antiseptic qualities of the bile. Finally, a last element comes to the aid of the fermentative processes, especially in the stomach; I refer to *mucus*, always present in the stomach at the time of digestion, and in the majority of gastric diseases permanently present and in large quantity. It was formerly believed to be endowed with saccharizing properties, and of itself alone capable of producing the organic acids which we have investigated; its rôle to-day, however, has devolved upon the ferments and microbes. It contents itself, and this is sufficient, with furnishing them a medium of a constant alkalinity which protects them against the action of the hydrochloric acid contained in the gastric juice.

Minkowski[4] thus sums up the effects of the gastric fermentations: "They give rise to products of a nature to irritate the mucous membrane and there provoke a catarrhal condition; they develop gases, sometimes in great quantity, are a cause of malaise

[1] M. Macaigne, *Thèse de Paris*, 1891.

[2] Hanot, "De l'ictère grave hypothermique," *Arch. gén. de méd.*, avril, 1893; "Ictère grave colibacillaire," *Soc. de biol.*, 17 février, 1894, et *Soc. méd. des hôpitaux*, 4 mai, 1894.

[3] Boix, "De l'action hypothermisante du Bacillus coli com.," *Mémoire à la Soc. de biologie*, 27 mai, 1893, et 8 juin, 1893.

[4] Minkowski, *Mittheil. aus der med. Klin. zu Konigsberg*, Leipzig, 1888.

to the patient, and aggravate the gastric atony. Among the substances produced, certain ones exercise a toxic influence and the fermentations of the albuminoids may engender bases which neutralize the hydrochloric acid."

It was not irrelevant to pass in review, at least in a summary manner, the poisons of the alimentary canal. An etiology careful of the truth must justify the doctrine, henceforth sovereign, of auto-intoxication, and not take up the subject of pathogeny with insufficient knowledge of the causes of disease.

CHAPTER III.

CONDITIONS WHICH FAVOR THE PRODUCTION OF THESE POISONS.

It is now fitting that we should analyze the conditions under which the abnormal fermentations arise, and ascertain, among the diseases of the stomach or intestine, those which realize these conditions. Two causes play the principal rôle: *motor insufficiency* and *stagnation of the ingesta*. The insufficiency of hydrochloric acid as an anti-zymotic renders the diminution of the secretion of the gastric juice less important; somewhat less important also are the alterations of the mucous membrane.

It is the *dilatation of the stomach* which we must especially consider. M. Bouchard thus defines dilatation: "Every stomach which does not contract when it is empty is a dilated stomach." This definition, absolutely correct from an anatomical point of view, is not perhaps sufficiently comprehensive, and if it leaves it to be understood that the stomach which does not contract contains a chyme imperfectly elaborated and in process of fermentation, it does not say so.

M. Bouveret is more explicit. For him, dilatation of the stomach is "a permanent pathological condition which at one and the same time is characterized by increase of volume, diminution of tonicity, and existence of retention." By this definition the dilated stomach is distinguished from the large and from the insufficient stomach. More practical, MM. Debove and Rémond define dilatation as "an insufficiency of motor functions, so that this organ ordinarily contains in the morning, when the patient is fasting, food in marked quantity." They have endeavored to distinguish dilatation pushed to this extreme (in a physiological sense) from *simple distention* and *atony*. Rosenbach recognizes a certain degree of relaxation which he calls *gastric insufficiency*. Boas has proposed the term *myasthenia*. In these cases there is a more or less marked diminution of the tonicity and elasticity of the muscular tunic; clapotage (splashing) can be readily in-

duced during the whole or the greater portion of the digestive period; but, be the stomach small or large, it is empty in the morning or only contains secretory products, mucus or gastric juice.

It seems to me that it is not particularly important to differentiate in words the degree more or less marked of the stomachal dilatation and alimentary stasis. Where does atony end and dilatation commence? At what hour must the stomach be completely empty in order that we may decide if there is or is not stagnation of the food?

One sentence appears to me capable of truthfully expressing, from the stand-point of pathogenic result, the condition of a stomach the motor functions of which are defective, and I would willingly accept this definition, if it is one; *stomachal dilatation is a constipation of the stomach.* This definition comprehends at one and the same time: asthenia of the muscular tunic, the alimentary stasis which follows it, and the abnormal fermentations which are its consequence.

It considers the word dilatation in its broadest sense and establishes a connection, too frequently neglected, between the condition of the stomach and that of the intestine. It is a mistake, says Lasêgue,[1] by our arbitrary analysis to isolate gastric from intestinal pathology. These two portions of the alimentary canal are conjointly responsible and we may say that *auto-intoxication of gastro-intestinal origin finds its sufficient reason in constipation.* Whatever may be the cause of it—pyloric obstruction of every kind, chronic gastritis, primitive or nervous atony, excess of foods or drinks—stomachal dilatation with stagnation of ingesta is, the same as intestinal atony with coprostasis, a source of injurious substances so much the more easily absorbed as the stasis is longer.

M. Bouchard has translated this into clinical language as follows: "The appetite is generally preserved; it may be increased. The majority of individuals with dilated stomachs eat heartily. Ingestion is not at all painful, but at the end of two, three, or four hours the stomach is distended; there are eructations at first inodorous, then *sour*, sometimes *fetid;* a sensation of weight, of burning in the epigastrium, some pyrosis, regurgitations of which the acid odor *demonstrates* the reality of the abnormal fermentations which are taking place in the stomach, for hydrochloric acid has no sour smell,—this is due to acetic acid.

[1] Lasègue, *Introduction au Traité des maladies de l'estomac de Brinton*, 1870.

"The fæcal matters are generally pasty, offensive, acid; although soft, they are expelled slowly and with difficulty. We can assure ourselves of the fact that their acidity is due to the predominance of acetic acid. The consequence of this development of acid along the whole length of the alimentary canal is an inflammatory condition. We observe catarrh of the stomach and ulcerative gastritis, to which the patients may succumb after having had a *bad stomach* for twenty-five years: these are the so-called cases of false cancer, or malignant gastritis without tumor. The large intestine is inflamed; glairy secretions surround the fæcal matters, sometimes some blood is present (membranous enteritis)."[1]

To the dilatation of the stomach, properly speaking, after a certain time is added chronic gastritis which contributes, through the plentifulness of the secreted mucus, to the production of abnormal fermentations. It is to M. Hayem especially that is due the great credit of having shown that the termination of the majority of the inflammations of the stomachal mucous membrane is a mucous transformation of the glands of the stomach. We know that, from the point of view of pathological anatomy as well as from a physiological stand-point, we may divide the cellular elements into two apparatuses.

The first, the *muco-pyloric*, comprehends: first, all the epithelium of the surface which furnishes the mucus (caliciform or goblet cells); and second, the principal cells of the pyloric glands, which do not fabricate mucus as we have supposed, but of which the secretion seems devoid of digestive properties, although containing some ferments. The second is the peptic apparatus, comprehending the whole of the glands containing both the chief and parietal cells.

Now, what takes place in the majority of the cases of gastritis either immediately, in the gastritis termed mucous at the first onset (d'emblée), or in the long run in hyperpeptic gastritis? *A mucous transformation* of the glands of the stomach. The surface epithelium is hypertrophied, and there is cellular proliferation of its deep layer. At the bottom of the funnel-shaped tubes of the neck of the glands, some cellular buds shoot forth which penetrate the meshes of the areolar tissue. From these buds new glands are soon formed which in part take the place of the altered or atrophied peptic glands, so that it is a new mucous membrane

[1] Bouchard, *loc. cit.*, p. 171.

which has replaced the old, and, physiologically, there results from it a destruction of the digestive properties of the gastric juice (Hayem).[1] This anatomical discovery (and it is manifest upon the preparations of M. Hayem which I have had the honor to examine in his laboratory) gives a clear explanation of a fact which clinically had been observed for a long time: a diminution of digestive functions in connection with a very large quantity of mucus. "To a first stage of acid catarrh," say Debove and Rémond,[2] "(whatever may be the origin of the gastritis), succeeds little by little a diminution of the hydrochloric secretion which is replaced by a neutral or alkaline mucous liquid, still rich in pepsin; but this ferment itself soon disappears, and the gastric contents are no longer anything but a mucus turbid from white globules and desquamated cells."

These authors besides say that chronic gastritis "is accompanied by a hyperactivity of the mucous glands, the secretory products of which cover the gastric walls with a glairy coating." We must not forget that chronic gastritis, under whatever anatomical form it presents itself, causes an alteration of the muscular tunic,—atrophy or sclerosis. It would be useless to speak in detail of the diseases of the stomach in which abnormal fermentations are encountered. It would be necessary to study them all one after the other, since all terminate in atony and chronic gastritis. Says M. Hayem, even the so-called nervous dyspepsias always commence with a gastropathy. I will confine myself to quoting here a page from his *Clinical Lectures:* "They have said of nervous dyspepsia that it was a romance. Alas, no, not from a semeiological point of view. No description of distressing symptoms can be more precise than that given us by those suffering from gastric disease. But it is a tower of Babel; it is the chapter in which, besides some cases with which I shall soon acquaint you, we find other cases illy understood, incorrectly interpreted, incompletely investigated; I might almost dare to say, wrongly diagnosed. Dyspepsia is the semeiological expression of the gastropaths who suffer. It may even be solely constituted by remote symptoms, in some sort extra-stomachal, the gastropathy proper remaining latent. If you make of this dyspepsia a primary nervous condition upon which the gastric affection depends, then, contrarily to what takes place with other organs, all the

[1] Hayem, *Bulletin médical*, 1894, No. 6.

[2] Debove et Rémond, *loc. cit.*, p. 216.

lesions of the stomach which I have described to you, all, without exception, are secondary, and the consequence of a primary nervous condition.

"We must make a choice: gastropaths are neuropaths or they have an organo-pathic affection. The true relationship of the morbid evolution is generally not recognized. Sufficient attention has not been paid to the true cause of gastric affections, to the good nature (bonhomie) with which the stomach remains diseased for a long time without manifesting in a perceptible manner its condition of organo-pathic suffering. We ignore these latent gastric conditions, of which I was careful to speak to you at the very beginning of your studies, and we only recognize the morbid state when it becomes a *dyspeptic condition.* We commonly say that the dyspepsia induces the organic disease of the stomach. Exactly the reverse is the case: the organic disease commences first, and the dyspepsia follows. Dyspepsia, with its sombre cortege of nervous phenomena, is one of the consequences of the stomachal alterations with which I have made you familiar. It is far from being the only danger incurred by gastropaths, and I can assure you, basing my opinion upon a considerable number of clinical cases, that the gastropathies open the door for a great number of chronic affections.

"Has not our patient, in addition to his nervous troubles, incipient renal disease and a bad condition of the liver? In his very remarkable work upon stomachal dilatation, my colleague, M. Bouchard, mentions some cases similar to those which I have myself observed, and I am happy to agree with him in regard to this point, that a certain number of individuals with dilated stomachs are not yet dyspeptic, but only destined to become so.

"It follows from my special studies that this latent dilatation is the consequence of a developing disturbance of digestion. It is only the second link of a chain of which the first is the lesion of the stomach, and of which later on the third will be the dyspepsia. People do not have dilated stomachs without cause, nor suddenly. The dilatation indicates a condition of somewhat long standing. Examine these so-called atonic stomachs, affected, according to the theory, with motor disturbances of nervous origin; you will find them endowed with a remarkable contractility. As soon as the tube enters them they will vigorously eject their liquid contents. We may even say that they are sometimes in a state

of motor excitation. True atony, stomachal myasthenia, is relatively rare; it is one of the remote consequences of organic disease.

"To recapitulate, here is what I think I should say in reference to clinical observation: we frequently come into the world with a weak stomach, organically little fit to resist the numerous causes of irritation which assail it. If I had to treat to-day of the etiology of the gastropathies, I should have to cite to you many causes which would explain this innate weakness, which we recognize for many other organs or systems, and which we seem to ignore when the alimentary canal is concerned.

"In the very first months of life, gastro-intestinal affections are frequent and of the greatest importance, as from all time they have been the principal cause of infant mortality. Most frequently our patients are not informed in regard to the ailments which they have had during this epoch, their parents either not having remembered or having said nothing in regard to them. And, nevertheless, these first injuries of a mucous membrane yet in process of development may be sometimes indelible. Childhood comes disturbed by acute infectious diseases, producing gastric disorders and frequently becoming the occasion of an inopportune medicinal interference. Without enumerating the causes of gastritis, what may we not say of the peculiar diets to which a great number of children are subjected, even in rich families? Do you know that gastropathies are extremely frequent with children five and six years old; that some of them present the same forms of gastropathy as adults? Very soon the studies commence and the influence of the deplorable school hygiene. An alimentation vicious and coarse or, on the contrary, in certain mediums, too plentiful and too nitrogenous, insufficient mastication, work directly after or a little time after meals, the body bent double so as to make the liver rest upon the pylorus or duodenum, the confinement in an impure atmosphere, the lack of exercise—are these facts not sufficient to explain the development of gastropathies? And note, moreover, that at this age stomachal affections are apparently rare. The child is puny, poorly developed, but it does not complain. However, you will find that it has already a dilated stomach with clapotage.

"We reach the age of puberty when all the causes of gastric disease are going to be accentuated. At this epoch, in which the organic development will require the best general and alimentary

hygiene, in which the appetite is increased in proportion to the needs of the economy, they set to work to prepare themselves for examinations, they abridge the time devoted to recreations and meals; an intellectual effort is required which interferes with and interrupts the play of the nutritive functions.

"In certain mediums the vices commence to produce their fatal effects: tobacco and alcohol enter upon the scene. With the young girl, we must take the corset into consideration, which mechanically impedes the gastric evacuation. Notice, besides, that these different causes of gastric irritation or of functional annoyance are frequently present with individuals predisposed to nervous affections, with those suffering from nervous debility, etc.: that to these causes is added cerebral overwork, which we must consider in order to comprehend the form under which the stomachal affection is going to present itself. It is, in fact, frequently at puberty or a little after that the gastropathy manifests itself outwardly, so to speak, and frequently also its first manifestation will be in the form of a dyspeptic neurasthenia. The clinical form of the disease is then going to depend, not solely upon the lesion of the stomach, but upon the individual, upon his morbid pre-dispositions, upon his own mode of reaction. Various causes acting upon the stomach will have already produced the gastropathy; he, the patient, will create his dyspepsia in his own way by imprinting upon it his individual seal." [1]

After this long and suggestive quotation, any digression in regard to dyspepsias of long standing would be, it seems to me, superfluous. *Dyspepsia is a syndrome*, and it is in the profound study of the patient and of his alimentary canal that we shall be able to unveil the true cause of the disease, while remembering however these two aphorisms of MM. Debove and Rémond [2]: "There is no constant relation between the disturbances of the functions of the stomach and the sensations of the patient." "There is no constant relation between the cause and the form of the dyspepsia."

Independent of dyspepsia and gastritis, the forms of which lend themselves a little to the interpretations of each author, there are three well defined morbid types: acute gastric catarrh, (embarras gastrique), ulcer of the stomach, cancer of the stomach.

[1] Hayem, *Bulletin médical*, 1894, No. 31.

[2] Debove et Rémond, *loc. cit.*, p. 169.

The autopsies of Laboulbene,[1] of Ziegler,[2] of Sachs,[3] etc., have proven that, at the very commencement, the proportion of mucus increases in gastric catarrh, the muciparous glands being swollen. At the same time, the gastric secretion is arrested and the acids of fermentation are formed, whilst the micro-organisms multiply. Ewald, examining the matters vomited by himself and also those vomited by several of his patients while suffering from acute gastric catarrh, has found that the filtered liquid, devoid of hydrochloric acid, contained traces of lactic acid and quite an amount of fatty acids.

Senator, in a case of gastric catarrh of two days' duration, observed the presence of sulphuretted hydrogen in the urine. We think that the repetition of accidents of this kind produces a positive lesion of the mucous membrane and a permanent dilatation of the stomach. In *ulcer of the stomach*, the mucous membrane, even remote from the ulcer, is rarely intact; we ordinarily find some chronic gastritis or, as M. Hayem says, some hyperpeptic parenchymatous gastritis, and as in Reichmann's disease, a habitual hyperchlorhydria.

These patients are then exposed to the same phenomena of dilatation and stasis as the preceding ones. In *cancer of the stomach*, we find gastric dilatation and the abnormal fermentations with absence of HCl in almost all the cases. These phenomena are at their maximum in cancer of the pylorus; besides there is always a co-existing gastritis, acute or chronic, catarrhal and interstitial (Rosenheim, Mathieu).[4] Boas[5] makes the presence of an excess of lactic acid in the stomachal liquid, after the test meal, a sign of gastric cancer. The ulceration of the tumor is a gate of entry for the microbes and the stomachal toxic products. M. Hanot[6] has called attention to the *septicæmic form* of cancer of the stomach with considerable painful swelling of the liver. Lastly, the fever of cancerous patients, due perhaps to the toxic substances produced by the neoplasm itself, may also be attributed to the absorption of gastro-intestinal poisons proceeding from abnormal fermentations.

In order to finish this chapter, there yet remains a word to say in regard to the condition of the stomach in certain diseases.

[1] Laboulbene, *Anat. path.*, 1879.

[2] Ziegler, *Allgem. und. spec. path. Anat.*, 1891.

[3] Sachs, *Inaug. Dissertation*, Breslau, 1886.

[4] Mathieu, *Arch. gén. de médecine*, 1889.

[5] Boas, *Deutsch. med. Wochenschr.*, 1892, No. 17.

[6] Hanot, *Arch. gén. de médecine*, 1892.

Pulmonary tuberculosis is accompanied, especially in the latter part of the disease, by chronic gastritis with or without amyloid degeneration. Marfan[1] has observed this gastritis in eighteen out of twenty-seven tuberculous patients. It is probably of infectious origin.

The swallowed expectoration contains not only the tubercle bacillus, but, in addition, the microbes of suppuration and various irritant matters. Their injurious action upon the gastric mucous membrane is so much the greater as the nutrition is disturbed by the fever and general infection of the organism.

Typhoid fever has also some gastric accidents[2] here comprehending dilatation, which likewise may precede and pave the way for this disease (Bouchard).[3] The stomachs of *diabetics* are not indemnified against lesions. Several authors, Cantani[4] in particular, have observed interstitial gastritis with glandular atrophy. It is probable that this condition of the stomach is connected with the development of the diabetic cachexia. We are also familiar with the digestive disturbances of individuals suffering from heart disease. It is the common chronic gastritis which we encounter most frequently. Lancereaux[5] has shown that there is a venous hyperæmia of the coats of the stomach. More recently Hautecœur[6] has investigated the alteration of the stomachal chemism in the clinical forms of the cardiac gastropathies.

The secretion is generally diminished, the total acidity is slight, the proportions of free and combined HCl are very much below the normal, and if the total acidity is great, it is due, in great part, to the acids of fermentation. The repeated purgatives which they administer to those suffering from asystolia, particularly drastic cathartics like the German *eau de vie*, may contribute to the development of gastric catarrh. How many patients affected with *gastro-intestinal uræmia*, especially the slow form[7] are considered and treated as dyspeptics! Patients with Bright's disease, whose kidneys function badly, force their stomachs to perform a vicarious function. Pilliet[8] has shown that the lesions of uræmic gas-

[1] Marfan, *Thèse de Paris*, 1887.
[2] Chauffard, *Thèse de Paris*, 1882.
[3] Bouchard, *Thèse citée.*
[4] Cantani, *Le diabète sucré*, trad. de Charvet, Paris, 1876.
[5] Lancereaux, *Atlas d'anat. pathol.*
[6] Hautecœur, *Thèse de Paris*, 1891.
[7] Pougis, *Thèse de Paris*, 1877.
[8] Pilliet, *Soc. de biologie*, 1887.

tritis are no other, histologically, than those of common chronic gastritis. Lastly, various chronic intoxications, such as morphinomania (Hitzig),[1] markedly diminish the secretion of gastric juice which is very poor in HCl. By this rapid *exposé*, we may see how frequent are the cases in which are combined the three principal factors of auto-intoxication: *gastric atony*, *alimentary stasis*, *chronic gastritis*. The state of the intestine in the various affections of this organ and in the course of the diseases of which we have just spoken, particularly in cancer of the stomach and in tuberculosis, would show us that this portion of the alimentary canal is not the least important from the point of view of the production of toxic matters and of their absorption. To undertake this study would only be a repetition.

[1] Hitzig, *Berl. Gesellsch. f. Psych. u. Nervenkr.* Nov., 1872.

PART II.

The Liver of Dyspeptics.

CHAPTER I.

THE LIVER AND ITS POISONS.

Stich was astonished, says M. Bouchard, at the fact that there were so many poisons in the alimentary canal, and so few toxic accidents. We ourselves are less surprised, as now, besides the eliminative action of the kidneys, we are acquainted with that wonderful function of the liver by means of which the organism wards off the assaults of poisons of every kind, whether introduced from without or elaborated in the human economy itself.

Although in 1873, Heger[1] announced the fact that the liver retains a portion of the vegetable alkaloids which traverse it, it is to Schiff[2] that is due the honor of having first carefully studied this property of the hepatic gland; and this discovery, as remarkable as that of glycogenesis, places its author by the side of Claude Bernard in the history of the physiology of the liver.

Since that time numerous authors have thoroughly investigated this question. M. Bouchard has greatly contributed to its progress, and the very important thesis of his pupil, G. H. Roger,[3] has markedly increased our knowledge in reference to this important physiological point.

For a long time we had known that the liver renders certain substances suitable for the nutrition of our cells, which would not have been available for that purpose if they had not first undergone a metamorphosis.

"Situated, as it were, at the principal entrance of the human economy," says Blondlot,[4] "the gate through which must pass

[1] Heger, *Thèse d'agrégation*, Bruxelles, 1873.

[2] Schiff, *Arch. des sciences phys. et naturelles*, Genève, 1877.

[3] G. H. Roger, "Action du foie sur les poisons," *Thèse de Paris*, 1887.

[4] Blondlot, *Essai sur les fonctions du foie et de ses annexes*, Paris, 1846.

all the nutritious substances arriving from without through the portal vein, the liver arrests their progress, in order to make them undergo a radical decomposition." But, if any noxious substances demand admittance, the hepatic cell, by virtue of a sort of selection reserved for its protoplasm, retains or transforms them: either in order to return them gradually to the circulation in harmless amounts or in forms less toxic, thus reaching the renal filter which eliminates them; or they are removed by the biliary vessels, most generally after they have been converted into substances less easily absorbed by the intestine.

This protective rôle is comparable to that played by the white blood globules with other injurious substances. We may say that the hepatic cells are to poisons that which the leucocytes are to micro-organisms and other foreign microscopic bodies. Their function, in regard to these poisons, is a sort of chemical phagocytosis. The importance of the hepatic gland was well understood by Galen, who considered the liver as the central organ of life. "This vast conception," says Poucel,[1] from every stand-point appears to be so true that, in my opinion, *the liver is to vegetative life that which the brain is to the life of relation.*"

However this place of honor is dangerous, and the liver may profoundly suffer from the attacks of the noxious substances, against which it is its duty to protect the organism. It may be found unequal to its task, as the poisons which traverse it may be in too great quantity, or the organ itself may be affected with a congenital or acquired inferiority. Again, we must distinguish in the liver, from the point of view of susceptibility, the various parts which compose it. The hepatic cell may function perfectly and render harmless many a substance which will exercise an irritant action upon the portal vessels; in other cases, a poison will arrive at the liver in such quantities that the cell will be destroyed before the different passages have had time to undergo any appreciable alteration.

The aphorism of Stahl, *vena porta, porta malorum*, does not apply solely to the economy in general; it is also true for the liver itself. The liver may be affected in other ways than by means of the portal vein: through the hepatic artery it participates in all the dyscrasias, in all the sanguineous infections—septicæmias, bacillæmias, etc.; through the ductus communis

[1] Poucel, *De l'influence de la congestion chron. du foie dans la genèse des maladies*, Marseille, 1883, p. 9.

choledochus, inflammation of the duodenum can easily extend to the biliary passages, and micro-organisms readily ascend as far as the canaliculi, if they are favored by the least retardation of the current of bile.

Nevertheless, the portal vein is the channel most open to noxious influences and also the most dangerous, because poisons thus arriving may act at the same time upon the three constituent portions of the hepatic organ: first upon the portal vein itself, extra and intra-glandular; second upon the hepatic cells; third upon the excretory passages, the canaliculi and the biliary canals. In fact, a poisonous substance carried into the stomach or intestine may provoke an intra- and extra-hepatic pylephlebitis. Once the poison is in presence of the hepatic cells, one of three things may happen: either the functioning of these cells will be normal and adequate to destroy or transform the poison, the whole evil being arrested in the afferent portal vessels; or their functioning will be inadequate, and then, if the amount of poison is very great, the cells will succumb; If the amount is not so large, insufficient to immediately alter the cells, they will be able to transform a portion of the poison, but the remaining portion may pursue two different paths: first, that of the intra-lobular veins, and there will be, independent of the bi-venous sclerosis, a slow intoxication of the whole economy; second, that of the biliary canaliculi, which will convey the poison outwardly but not without injury to themselves as, like the afferent vessels, they will experience its irritative effects.

The angio-cholitis may be even more extensive than the periphlebitis and, in addition, there may be a new formation of biliary canaliculi. All this, certain chemical poisons can accomplish as well as microbian toxins. Things may not go so far, especially at the commencement of the affection, and we witness a simple congestion of the liver of greater or less duration; sometimes, however, it may be permanent.

CHAPTER II.

CONGESTION OF THE LIVER OF GASTRO-INTESTINAL ORIGIN.

THE relations between diseased conditions of the alimentary canal and congestion of the liver, long ago attracted the attention of physicians, who had observed an increase of the volume of this organ with dyspeptics, employing the word dyspepsia in its broadest sense. Portal[1] says that great eaters ordinarily have an enlarged liver. Casimir Broussais,[2] fils, while studying chronic duodenitis, clearly observed the effect of this disease upon the liver.

"By the touch," he says, "we can distinguish a certain swelling, the seat of which it is impossible to precisely determine, from the normal resistance of this region (duodenal). This tumefaction increases, is very soon visible, and by palpation we can ascertain that the anterior border of the liver extends beyond the false ribs. There is evident obstruction of this organ. The tumefaction remains and may make such progress that the liver descends as far as the umbilicus and even sometimes to the crest of the ilium."

At the present time we are far from interpreting things in the same manner as did the elder and younger Broussais, or from invoking, in order to understand the relations of duodenitis and congestion of the liver, the famous law of Bichat: "The action of glands corresponds to the stimulation of the surfaces where their excretory canals end."

For a long period, the authors of works upon dyspepsia or diseases of the stomach paid no attention to the condition of the hepatic gland. We can convince ourselves of this fact by reading Cullen, Barras, Chomel, Trousseau, Beau, Guipon, Nonat, Bayard, Brinton; G. See, Gubler, and Raymond also only speak of the liver in order to point out the effect of its diseases upon the stomach. We must, however, make an exception in favor of Andral.

[1] Portal, *Observations sur la nature et le traitement des maladies du foie*, 1813.

[2] C. Broussais, *Thèse de Paris*, 1825, page 27.

As a scrupulous observer, in an autopsy he would not pass by any microscopic detail, and in two cases of ataxo-dynamic fever, with gastro-intestinal lesions, he noted that "the liver had a pink color and a remarkable thickness." "But," says he, "this lesion was purely accidental and very probably had no connection with the disease from which the patients succumbed."[1]

He becomes more interesting in the second volume and asks the question,[2] "If a great number of diseases of the liver do not recognize for their cause, for their point of departure, a gastro-intestinal affection. An observation of the symptoms leads us in this respect to share the opinion of M. Broussais, who admits that, in a majority of cases of phlegmasia of the liver, there is duodenitis in the first place.

"An examination of the causes, under the influence of which chronic hepatitis is quite frequently developed, would beside lead us to place its point of departure in the alimentary canal. In fact, it is the result of our observations, that the majority of individuals who have died of chronic hepatitis have used alcoholic liquors to excess. We easily comprehend how the habitual stimulation of the digestive mucous membrane by these beverages, through continuity of tissue, was extended to the mucous membrane of the excretory canals of the bile and from thence to the hepatic parenchyma. Besides it has been experimentally demonstrated that alcohol introduced into the digestive passages of an animal is there rapidly absorbed.

"Now, borne directly into the liver by the mesenteric veins, cannot the alcoholic molecules there directly cause an intense irritation of this organ? Lastly, it is possible that, under certain circumstances, the irritation is propagated from the intestines to the liver through the means of a venous inflammation. This is the opinion of M. Ribes. We know that careful dissections have informed this learned anatomist that erysipelas is frequently accompanied by a phlegmasia of the veins; and, from this he thinks that it would not be impossible that, in certain gastro-intestinal inflammations, the veins which originate at the surface of the mucous membrane should become inflamed; that this inflammation should spread from the small mesenteric veins to the trunk of the portal vein and be thus extended to the parenchyma of the liver."

[1] G. Andral, *Clinique médicale*, 3 édit., t. i. *Maladies de l'abdomen*, t. i., observations vi. et xvi., p. 612, 1834.

[2] *Ibidem*, t. ii., p. 305 et suivantes.

Two clinical cases follow: one of an individual who died of gastro-enteritis, the post-mortem examination revealing a punctated injection of the gastric mucous membrane, and of the lower third of the ilium and cæcum; there was also an intense redness of the internal surface of the inferior mesenteric vein, of the trunk of the portal vein, and of all its hepatic ramifications. The liver itself was large, very red, engorged with blood, and friable. The other case was that of a subject who died of cancer of the pericardium, in which there was a red induration of the liver, its veins being a bright-red color on their internal surface, and, in the alimentary canal, there were signs of a chronic phlegmasia, such as a mammillated appearance and a brownish color of the gastric mucous membrane. The duodenum was of the same color, with some ulcerations and a remarkable development of the follicles, with a black coloration around them towards the end of the small intestine, in the cæcum, and the commencement of the colon. Andral remarks in regard to the latter case, "that the disease commenced with a diarrhœa which appeared to be the only affection for at least a year. It was only at the end of this period that some pain was felt in the right hypochondrium. The patient twice had jaundice, and later on ascites finally developed itself. This succession of symptoms at least indicates that the disease of the liver was consecutive to that of the intestine."

Here, very clearly presented, is a very contemporaneous pathogeny. In the same volume, Andral gives a very interesting case, questionable, I must confess, as to the nature of the hepatic affection, but which we may present as a type of *chronic congestion of the liver*, consecutive to some undeniable gastro-intestinal lesions. Andral simply calls it a case of general hypertrophy of the liver with chronic gastro-duodenitis; no jaundice.

Case I (Andral).[1]

A compositor, aged forty-three years, enters Charity Hospital in the following condition: great emaciation; face pallid; copper-colored spots upon the skin of the thorax, back, and limbs. The sharp edge of the liver can be felt in a very distinct manner a little below the level of the umbilicus, and extends to the left of it about two or three finger-breadths. In all the space included within two supposed extended straight lines, one reaching from the cartilaginous border of the false ribs on the left side to a little

[1] Andral, *loc. cit.*, tome ii., p. 374.

below the umbilicus and the other extending from this latter point to the right flank, we feel a hard body with smooth surface, which is terminated inferiorily by the sharp edge mentioned above, the limits of which to the left cannot be exactly indicated, and which above appears to be continued behind the ribs. There is no question that this body is the hypertrophied liver.

The tumor which it formed was completely indolent. But when the patient ate anything or drank any undiluted wine, he felt a painful sensation at the epigastrium, which sometimes was only temporary, and sometimes was prolonged for several hours. The tongue had its natural appearance, save that it was somewhat paler than usual. There was habitual loss of appetite, without increase of thirst, without nausea or vomiting. The stools were infrequent, the fæcal matters being hard and brown; the urine scanty, red, and full of sediment.

The pulse was ordinarily rapid, without there being any heat of the skin. The patient tells us that, six years before his entrance into the hospital, he had taken a great deal of Van Swieten's solution and a large amount of a decoction of sarsaparilla; that these remedies not relieving him of the large and indolent buboes which he had in his groin, as the result of the chancre on his penis, he had taken a certain amount of sulphuric acid united with cream of tartar. But, after several days' employment of this remedy, he was suddenly taken with a severe pain, tearing, in his epigastrium, the appearance of which was accompanied by a temporary loss of consciousness and epileptiform convulsive movements. During the five days following the patient kept his bed; the epigastric pain gradually lost its first severity; but, dating from this epoch, his digestion was difficult and painful, his appetite was lost, his strength and flesh have gradually grown less.

The patient had not perceived the presence of the tumor formed by the liver, which is not astonishing, as it formed no projection of the abdominal walls and was not painful. This individual lived nearly six weeks after his entrance into the hospital. During this time we saw him gradually grow thinner and weaker. Properly speaking there never was any fever. During the last ten days of his life, he vomited at four different intervals a large amount of a black matter resembling coffee-grounds: thenceforth, alteration more and more profound of the features of the face, chilliness of the extremities, drowsiness, and death.

Autopsy.

The abdominal walls having been raised, the first object which struck us was the enormous volume which the liver had acquired. It covered a large portion of the intestines, extended downwards to a little above the crest of the ilium, and reached a good deal beyond the linea alba. Its volume relatively to that of the other organs was similar to that which we observe with the fœtus. Its external surface showed the two natural substances of the liver very clearly. In the interior, we likewise found them. There was nothing abnormal in the texture of this organ. It was neither harder nor softer than ordinary; upon incision only a moderate amount of blood flowed from it. The gall-bladder contained no more bile than usual; this bile was of a clear yellow color. Nothing unusual was remarked in the hepatic canals, cystic and choledochic.

The stomach, small and contracted, was entirely concealed by the liver. Its walls were hard to the touch. Its internal surface was of a slate-gray throughout its whole extent, and mammillated. This appearance depended upon the considerable hypertrophy which the mucous membrane had undergone. This hypertrophy was unequal in different parts of the stomach; where it was very pronounced, its presence was announced by a species of pimples, or nipples, and between them there were some depressions in which the mucous membrane was somewhat thinned. The submucous cellular tissue participated a little, towards the pylorus especially, in the thickening of the membrane which covered it.

The duodenum presented on its internal surface the same slate-gray tint as that which we found in the stomach. The remainder of the alimentary canal offered nothing remarkable. The spleen was not large, of average consistence, such, in a word, as it presents itself when we regard it as being in its normal condition. The supra-renal capsules appeared to us as remarkable by their great development. The urinary apparatus was healthy. A very large amount of black coloring matter was deposited in the cellular tissue, either interlobular or intervesicular, of the lungs; there was also a great deal of it in the bronchial ganglia. We carefully examined the copper-colored spots with which several parts of the skin were covered. They were only found between the epidermis, which was not at all colored, and the cutis vera, which was likewise not colored. They were situated in the rete mucosum, that portion of the skin which, in the negro, secretes the dark coloring matter.

The remarks of Andral in regard to this peculiar case are a little antiquated; but they terminate in this very logical conclusion: "It is probable that the hypertrophy of the liver was consecutive to the gastro-duodenal inflammation." In fact this is what we should have a right to believe, even if the subject had syphilis, for I do not know with what known form of hepatic syphilis we could connect the liver described by Andral.

Perhaps also it was an instance of true cirrhosis, and this case would be in this event superposable to those which we shall find in the following chapter; but in the absence of any histological examination, I have preferred to consider it as an example of chronic congestion of the liver. From a work by George Budd, in all points remarkable, and which marks a new era in the history of diseases of the liver,[1] we quote the following paragraph: "All alcoholic beverages, all the substances which may be found in our food, and the noxious products of defective digestion, being surely soluble, are immediately, before they have entered the circulation and have been subjected to the influence of oxygen, conveyed to the liver, the circulation of which they more or less influence" (p. 65). And further: "We sometimes encounter them (the cirrhoses) with temperate persons, so that it is necessary that there should be some other causes than spirituous drinks. There may be some other substances among the immense variety of matters introduced into the stomach, or among the products of faulty digestion, which, absorbed into the portal vein, cause, like alcohol, adhesive inflammation (cirrhosis) of the liver. What these substances are is now a matter for discussion. In a great proportion of the published cases of cirrhosis, there are some organic lesions of the stomach, and in the goodly number of cases published by Andral, the disease seems to have commenced with vomiting and diarrhœa, which were, some time after, followed by ascites. Very many observations seem to show in a certain manner that the disease is occasionally produced by certain substances proceeding from defective digestion or from some errors of diet other than the excessive consumption of spirituous liquors.

"This conclusion is strongly supported by the experience of the physicians of the East Indies. Adhesive inflammation of the liver leading to an increase of its volume, to its induration, and consecutively to positive disturbance of its functions, is a common form of hepatitis of these countries, and seems to result in part

[1] George Budd, *On Diseases of the Liver*, third edition, London, 1857.

from the use of alcoholic drinks, which are especially injurious on account of the heat of the climate, in part from the great quantity of pepper and strong spices of different kinds, which the English consume in the East Indies" (p. 150 and following).

Thus it is as if fully convinced of the fact and not in the way of a hypothesis that Budd speaks of the rôle of the products of defective digestion in the genesis, not only of hepatic congestions, but also of cirrhoses of the liver. It is for him an evident thing which his clinical experience has demonstrated to him. For nearly forty years these pages have lain dormant without any one dreaming of going there to seek once more for the pathogeny of the cirrhoses, so long a time *macerated in alcohol.* Frerichs[1] barely suspects that the cirrhoses may have a more extensive etiology.

"Thus far," says he, "we have not been able to positively discover if, independent of alcohol, there are other ingesta which, carried by the blood of the portal vein through the liver, may excite in this organ an irritation capable of there developing a slow inflammation followed by induration." Leven[2] is the first contemporaneous writer who systematically treats this question. "When the dyspepsia," says he, "has lasted for a certain time, it frequently terminates by reacting upon the liver, producing congestion of this organ and causing hepatic colics."

He also cites some interesting cases: those only will be found here in which there is no question of biliary lithiasis.

Case II (Leven, case LXXIV).

S———, forty years old, stock-broker, sick for several years; complains especially of violent headache, of vertigo. He cannot traverse any place without being supported upon the arm of a companion. The whole left and median regions of the stomach are painful to pressure. He continually is passing off gas by the mouth and anus. His *stomach is filled with water* and he never vomits; he only has nausea. His fingers and arms are stiff. There is a species of contracture of the fingers. The hepatic region is painful throughout its whole extent: *the liver is large, congested*, as is frequent in cases of dyspepsia of long standing. This patient is pallid, melancholy, and believes himself obliged to

[1] Frerichs, *Traité pratique des maladies du foie.* Traduction de Duménil et Pellagot, 3 édit., 1877, page 302.

[2] Leven, *Traité des maladies de l'estomac,* 1879.

abandon his business. After two months' treatment he was entirely cured.

I will incidentally remark that the tetany was of gastric origin. Leven also mentions some other cases of it, one of which was followed by death in forty-eight hours.

Case III (Leven, case LXXVIII).

Madame L———, a widow, forty-four years old, has had three children. *Dyspeptic* for several years: the stomach bloats after meals. Eructations of gas and flatulence; stools every two or three days. If we press upon the epigastric region, no pain is produced; the liver is *swollen, extends three centimetres beyond the edge of the false ribs.* Throughout the whole right hypochondrium, pressure is very painful. This woman constantly suffers from frontal neuralgia and weakness of the legs.

Case IV (Leven, case LXXIX).

A———, for a year past, about five o'clock in the afternoon, feels some twinges of pain, some burning of the stomach. For several weeks he has had after meals some regurgitation of liquid; in the evening, about ten o'clock, he suffers from cramps in the stomach. He brings up water and gas. No sensitiveness in the region of the stomach but acute sensitiveness in the right hypochondrium. The liver extends four centimetres beyond the false ribs; it is voluminous. After meals the patient has pains in the jaws, and embarrassment of speech, and also some pain in the muscles of the limbs. He has been upon a milk diet for the last year but his condition has not been improved.

In 1883, Poucel, already cited, speaks incidentally of the alterations of the liver consecutive to abnormal digestion as follows: "Let us introduce into the portal system a substance less injurious than alcohol; lead or pus, or solely the *altered products of defective digestion.* These products, becoming part of the protoplasmic matter of the hepatic cells, will alter the chemical composition, the structure, and the function of these cellular elements before producing any disturbance in the general nutrition."

But it is Professor Bouchard who has most methodically investigated the condition of the liver in patients suffering from dilatation of the stomach. "Out of 389 cases of dilatation of the

stomach that have come under my personal observation," says he,[1] "I have noticed tumefaction of the liver in 23 per cent. This swelling is movable; it increases, diminishes, and disappears according as the dyspepsia grows worse or improves. Relapses are frequent. It is accompanied by soreness or a feeling of weight in the right hypochondrium and is sometimes complicated with jaundice. In the absence of the information which an autopsy would furnish us, these characteristics make me consider it as probable that this tumefaction is congestive. It is solely with patients affected with dilatation of the stomach that I have observed the congestion of the liver of chronic diseases."

This hypertrophy of the liver in chronic diseases such as diabetes mellitus, obesity, or gout, is it the result or the cause of the dyscrasia, of the faulty nutrition? It is impossible to decide this point at present, but it is probable that there is established a vicious circle between the defective nutrition and the diseased liver, these two factors influencing each other reciprocally.

Moreover, these patients are very frequently dyspeptics and there is nothing inconsistent in the hypothesis that their stomachs react upon their livers in order to produce or accentuate this congestion. Here is what Professor Bouchard says clinically in regard to it:

"Independently of the hepatic congestion which is connected with dilatation of the stomach, we observe, in certain chronic diseases, a tumefaction of the liver more considerable and more persistent, capable however of slow variations plus or minus, indolent, and never accompanied by jaundice. I am as yet unacquainted with the histological characteristics of this alteration of hepatic tissue. Its clinical characteristics and its pathological associations lead me to suppose that it is a question purely and simply of an increase of volume of the hepatic cells. In order not to decide prematurely, I give to this alteration the name of *large liver*."

Since this was written, M. Bouchard's list of cases has been increased. He has been kind enough to furnish me his unpublished figures for which I am exceedingly obliged. Of a total of 652 large livers, observed in men and women, 240 were coincident with dilatation of the stomach; 69 with digestive disturbances such as anorexia, constipation, vertigo, which makes a total of 309 large livers with dyspeptic patients, or a proportion of 48 per cent.

[1] Bouchard, *Soc. méd. des hôp.* 1884, et *Exposé des travaux scientifiques*, 1886, page 93 et 94.

The other large livers to the number of 343 were encountered with albuminurics (164), peptonurics (72), glycosurics (28), with obese patients (61), and with various other patients (16). If we take the statistics concerning dilatation of the stomach only, we see that out of 665 observed cases, large livers were encountered with 240 patients, which gives almost the same percentage. Here also is the table of cases of coincidence of dilatation of the stomach and large liver with other diseases:

Dilatation and enlarged liver	240
Dilatation + enlarged liver + peptonuria	44
" + " " + glycosuria	13
" + " " + diabetes	60
" + " " + obesity	25
" + " " + gout	12

M. P. Le Gendre,[1] out of 61 cases of dilatation of the stomach (dyspeptic or latent), has twenty-four times found hepatic tumefaction, permanent or intermittent, with smooth liver most frequently indolent, extending one to five finger-breadths beyond the edge of the ribs. In these cases, he has twice noticed transient or alimentary glycosuria. The majority of these subjects with dilated stomachs were of gouty ancestry or themselves presented many characteristics of this diathesis; several suffered from biliary lithiasis and gravel. M. Hayem [2] thinks also that affections of the stomach play a very important rôle in diseases of the liver. He observes in the first place that duodenitis is frequent in diseases of the stomach and that this duodenitis forms the bond of union between gastritis and certain hepatic irritations, especially those of the biliary passages. He next recognizes as a pathogenic cause acting upon the liver, the passage through the portal vein, not only of microbian toxins, but also of noxious substances which arise during the course of abnormal stomachal digestion; he especially incriminates acetic acid, which is almost constantly present with hyperpeptics.

"In regard to these different points," says he, "it is essential that some investigations should be made with the design of substituting precise ideas for simple probabilities." According to his clinical observations, hyperpeptic cirrhosis is frequently coincident

[1] P. Le Gendre, *Soc. méd des hôpitaux*, 26 fév., 1892.

[2] G. Hayem, Clinique in *Bulletin médical*, 1894, No. 49.

with hyperpeptic gastritis; atrophic cirrhosis, on the contrary, with chronic gastritis, manifesting itself by intense hypopepsia or even apepsia.

In another lecture,[1] M. Hayem reports a very instructive example of latent dyspepsia with stomachal dilatation and increase of the volume of the liver. This case is worthy of being reported in full, for it demonstrates how frequently diseases of the stomach are concealed under the mask of a nervous affection.

Case v (Hayem).

In February, 1891, I was consulted by a young man twenty-eight years old, a commercial traveller, of a puny appearance, with a tired and a little discouraged air. He informed me that he had been indisposed for more than ten years; that his indisposition, at first of little severity, had very much increased during the past two years. That of which he complained, was that he was not able to endure the air of close rooms, especially during the winter, when apartments are heated. Under these circumstances, he has flashes of heat; the blood rushes to his head and causes a painful sensation in his forehead and temples. His head, says he, feels as if it was in a vise, his eyes are injected with blood, his arteries beat forcibly, his vision is disturbed, his cheeks become red and burning; sometimes he can no longer remain in the room and is obliged to go outdoors and inhale deep breaths of fresh air.

His sensitiveness to confined air is such that it is impossible for him to work in a closed room. On the other hand, he ordinarily has cold hands and feet. These annoyances have spoiled his life; he is forced to isolate himself in order to take his meals, to avoid family or friendly gatherings, to deprive himself of the pleasure of going to the theatre, and it is painful for him to thus flee all social assemblages.

In addition, he is afraid of losing his position, of no longer being able to work. He has become impressionable, restless; his sleep is broken, not restorative, and he feels great general weakness. Thinking that the constipation from which he has suffered so long a time was the cause of his illness, every morning for six months he has taken a dose of sulphate of soda, and he has tried many other medicines without result. He complains of nothing else. He has a good appetite and claims that his digestion is

[1] Georges Hayem, *ibid.*, No. 31.

good ; he has not grown perceptibly thinner since he has been ill. In a case of this kind it was essential that there should be a careful examination. I found his tongue slightly coated, his belly a little tense, his *liver slightly swollen*, but not sensitive to the touch, and on auscultation of the heart, in addition I noticed a slight *bruit de galop* and a blowing murmur, a little rasping, loudest over the apex and prolonged on the side of the armpit. The patient, moreover, experiences some oppression and palpitation of the heart while ascending staircases. At my first examination his stomach did not appear dilated. I obtained neither clapotage nor succussion. Nevertheless, some days later, *the signs of dilatation were manifest.*

There is here a point to which I desire to call your attention. The first day, the patient came to see me a short time after eating ; at the second consultation, several hours had elapsed since he had taken his last meal. At different times, with this patient, I thought of the *possibility of letting a dilatation of the stomach pass unperceived, even when this dilatation was well pronounced*, when our examination is made immediately or a little after a meal when the stomach is full and tense.

Moreover, I have with other patients found the same state of affairs, which is liable to lead us into error. Lastly, I notice a feeble sexual development of the patient coincident with hypospadias and small testicles, almost infantile, and I think that this condition may have contributed to the patient's melancholy. An examination of this patient's gastric juice and urine furnished me the complementary information of this clinical examination. Examination of February 15, 1891 :

Total chlorine..... = 0.386
Fixed chlorine.... = 0.103
Combined chlorine = 0.284
Total acidity..... = 0.230
Free HCl..... = 0.036

Liquid rather abundant, filtering quite easily, well emulsioned. Peptones quite plentiful ; syntonin ; lactid acid reaction. As you see, it is a case of chloro-organic hyperpepsia. On account of the large amount of combined chlorine, coincident with a pronounced dilatation of the stomach, we might think that this condition, observed at the end of an hour, would terminate at a more advanced

period of digestion in a late hyperchlorhydria. This is the state of affairs in a large number of cases of chloro-organic hyperpepsia observed at the end of an hour after the test meal. With our patient this was proven later on, when, under the influence of a treatment which tended to improve his gastric condition, the chemical type became that of hyperchlorhydria d'emblée.

You will encounter a great number of cases of this kind. Examination made on December 24, 1892. Removal of the test meal at the end of an hour.

Total chlorine.... = 0.401
Fixed " .... = 0.063
Total acidity..... = 0.300
Free HCl..... = 0.160
Combined chlorine = 0.178

Liquid abundant, mucous. Peptones quite abundant; feeble acetic acid reaction. The analysis of the urine is not less interesting: it shows an increase of urea, of uric acid, and chlorides, and, as abnormal elements, a small quantity of albumin (less than a gram) without casts, and some *urobilin*. Before forming a decisive opinion in regard to this case, it was in addition necessary to inquire into the antecedents of the patient and also ascertain the conditions in which his affection developed itself. The father of this young man died quite young of albuminuria; his mother is yet living and healthy, but has had migraine almost all her life. He has one brother, dyspeptic, one uncle obese and another gouty. He himself has always been delicate, but quite well; he has never had rheumatism or gout. His diet at all times has been rather inferior. He has not been dissipated in any way, but his family is Jewish and their food is cooked with a great deal of grease and composed of heavy and indigestible materials.

He has been a commercial traveller for several years and frequently takes his meals in hotels and restaurants where the food is often far from being the best. He is a man of regular habits, very sensible, and has had neither cares nor sorrows. What must be our diagnosis? The nervous symptoms are evidently markedly predominant. They are the only ones in regard to which the patient is anxious and for which he has consulted us.

Taking for a guide the treatises on diseases of the stomach, you will see that, according to the most recent authors, these

symptoms resemble those which characterize *nervous dyspepsia.* This, however, is not my diagnosis. As soon as my examination was completed, I recognized the existence of a gastropathy of long standing, organic, with slow and insidious development, long ago having induced slowness of digestion and consequent dilatation of the stomach and constipation. In my opinion, it is this affection which has produced the general debility and which has reacted upon the nervous system and the nutrition. I have subordinated to it, not only the nervous phenomena, but also the *bad condition of the liver and kidneys.* On account of these latter complications, the case has appeared to me to be somewhat serious. I believe that I have discovered the origin of all this series of symptoms in the vicious alimentary hygiene which has exercised its influence since infancy upon an individual predisposed to chronic diseases by his hereditary antecedents, aad who presents the appearance of a weakling and almost of a degenerate. Perhaps, also, his stomachal affection is in part at least of hereditary origin, as a great number of clinical cases lead me to believe in the heredity of gastritis and especially of hyperpeptic gastritis.

In many families all the members are attacked by it: father, mother, children. My first care was to prescribe rather a severe diet, composed especially of milk and foods that were readily digestible. Later on, and according to the circumstances, lavage was practised, and the patient at different times took bicarbonate of soda. Hydrotherapy and abdominal massage were also employed.

In the first place there was some improvement of the cardiac symptoms: the blowing murmur soon disappeared. It undoubtedly was one of those bruits considered by M. Potain as extra-cardiac. Soon after, *the tumefaction of the liver disappeared, but for quite a long time after the retrocession of this organ, the urine yet contained marked traces of urobilin.*

The albuminuria only disappeared in October, and later on, after a trip, returned, only permanently ceasing in March, 1892. The nervous phenomena and the gastro-intestinal symptoms were much more obstinate to treatment. At different times the gastric dilatation and constipation disappeared and there was a lessening and even a suspension of the vaso-motor disturbances. But the patient could only take proper care of himself and have a suitable diet when he was in Paris. After each trip there was a longer or shorter relapse, more or less accentuated. In April, 1892, he

commenced to cough and grow thin and presented some signs of bronchitis of the right apex with dulness: a condition quite alarming, which made me fear tuberculosis. In September, 1893, notwithstanding the poor condition of his health, he was obliged to perform military duty. They sent him home at the end of five days, but this absence was sufficient to aggravate his situation for some time: the dilatation, which had disappeared, returned; the flashes of heat in his face came back and were accompanied by chilliness and a livid tint of the extremities.

The family of the patient being anxious in regard to his condition, I gave them to understand the necessity of his relinquishing his trips and, starting from this time, he commenced to improve. In November, 1893, the dilatation of the stomach finally yielded and has not since returned; but the vaso-motor disturbances lasted for some time longer. All manifestations of them ceased towards the end of November, 1893.

Now (January, 1894), the patient no longer complains, except of coughing and expectorating a little in the morning. The auscultatory signs, moreover, are not marked, and I have every reason to hope that this young man will escape tuberculosis.

The present treatises upon diseases of the stomach (Bouveret, Debove and Rémond, Mathieu, in treatise on medicine) only point out the possibility of the participation of the liver in dyspeptic processes. In a recent thesis, R. Millon,[1] a pupil of MM. Bouchard and Comby, takes the digestive disturbances of children affected with cutaneous diseases into consideration and the effect of these disturbances upon the liver. "The liver," says he, "with children frequently attacked by gastro-intestinal disturbances, is subject to astonishing variations of volume; these variations are enormous from one day to another; the livers of children are veritably elastic, to such an extent that an increase of volume manifesting itself one time by a lowering of the inferior border six centimetres below the edge of the ribs may be reduced, two days later, to three centimetres, even less, and again be reproduced three or four days after. *These transient and frequent hepatic congestions have seemed to us a strong confirmatory sign of a defective condition of elaboration of alimentary substances.*"

Here is a summary of the cases of Millon in which the condition of the liver was noted.

[1] R. Millon, *loc. cit.*

Case vi (Millon, case ii).

Louis P———, nineteen months old, a fine-looking child; suckled until sixteen months: since weaning, extremely plentiful diet; food in excessive amounts: the child is stuffed with soups, with starchy vegetables, mashed potatoes, carrots, etc.; he also eats enormously and gluttonously; in addition he is a great drinker. He ordinarily digests well but has a tendency to constipation and his passages smell horribly. His belly is large and distended. There is clapotage at the umbilicus several hours after eating; *the liver extends three and a half centimetres below the ribs.*

Case vii (Millon, iv).

Rene M———, fourteen months old, was born in poverty-stricken surroundings; his mother, tuberculous, was not able to nurse him. Has been fed on the nursing bottle with milk of poor quality; besides, they fed him other food very young. At the present time, besides a litre of milk which he drinks daily, they give him soups, meat; he drinks undiluted wine. He is also a puny and slender child who does not yet walk and has only six teeth. His belly is large, swollen; he has some clapotage at the umbilicus. He is ordinarily constipated and sleeps badly. *His liver extends a finger's breadth below the ribs.*

Case viii (Millon, ix).

Joseph C———, fourteen months. Child brought up on the breast, was suddenly weaned three days ago; has been fed greasy soups and porridges without having been accustomed to them. Forty-eight hours after weaning, appearance of patches of impetiginous eczema upon the face. *Liver reaches two finger-breadths below ribs.*

Case ix (Millon, x).

Lucienne B———, two and a half years. Eleventh child. Father a neuropath and a drunkard. Brought up on the bottle. Measles, whooping-cough, bronchial catarrh, convulsions; was early accustomed to eat every kind of food; has had diarrhœa. Tendency to rickets. The belly is enormous; *the liver extends downwards one and a half finger-breadths.* The child digests everything well which they give to it; she has no constipation, but the fæces smell badly.

Case x (Millon, xix).

Jeanne C———, twenty-nine months. Weaned too soon and very badly fed; is nourished almost exclusively on bread and cheese; a great drinker. Legs slightly incurved; chondro-sternal chaplet; belly hard, a little distended. Stomach slightly sensitive to epigastric pressure. *Liver a finger's breadth below ribs.*

Case xi (Millon, xxiv).

Louise S———, twenty-three months. Nursed by her mother until sixteen months. Since weaning and immediately after, an excessive amount of nitrogenous food: bouillon, meat, boiled beef, beef-steak; drinks water reddened with wine and a little pure wine. Profuse perspiration at night; habitual constipation, eructations, a little gastralgia, no dilatation; *the liver extends three centimetres below the costal border.* This child, since it was weaned, has had several attacks of general urticaria.

Case xii (Millon, xxv).

Marie P———, eight years. Brought up on the bottle. Has always been thin and delicate. Child manifestly dyspeptic, polydipsic; its stomach swells after meals and is painful but not dilated. *Liver reaches slightly below the false ribs.*

Case xiii (Millon, xxxvi).

Pierre S———, ten years old, small and puny, very thin. Nourished improperly. Has very little appetite and is fed almost exclusively with black coffee and café au lait. Great drinker, nervous, wakens frequently at night. Habitual constipation. Clapotage of the stomach as far as the abdomen. *Liver large, extending three centimetres beyond ribs.* After some months' treatment the liver resumed its normal dimensions.

Case xiv (Millon, xxxviii).

Louise F———, three years old; issue of a lymphatic and hysterical mother and of a nervous and alcoholic father. Since weaning, various digestive disturbances; moreover, very badly nourished; drinks a great deal of water between meals and eats every kind of food. She is a puny and very nervous child who has had frequent attacks of diarrhœa and whose belly is very much distended. *Her liver is enlarged.*

Case xv (Millon, xliii).

Raymond D———, three and a half years old. Child brought up in the country without any care; commenced bottle-feeding when six months old; weaned when a year old. Starting from this age has drunk everything, pure wine, coffee, etc. Tendency to rickets. No signs of dyspepsia; *the liver, a little large, extends a finger's breadth below the false ribs.*

Case xvi (Millon, xlv).

Theodore T———, three years, plainly rachitic. Mother markedly dyspeptic. Coarse food from a very early period: polydipsic. He is dyspeptic, has frequent diarrhœas, most generally fetid, some gastro-intestinal atony; his belly is constantly swollen; *his liver is large and reaches two centimetres below the costal border.*

It would perhaps be difficult to define exactly what we mean by congestion of the liver. "The congestive processes," says M. Chauffard, [1] "form in the pathology of each organ an illy-defined region, without precise limits, occupying so to speak the frontiers of the disease. At what moment does simple functional hyperæmia become pathological? In what cases does congestion, a simple anatomical state so common and so variable, deserve to be individualized into a morbid entity? For the liver, more than for any other organ, the line of demarcation is uncertain. That which we may say in a general way, is that hepatic congestion only becomes a disease by its intensity or by the repetition and the duration of the morbid stimulations."

It is very certain that it is a question, in the individual case, of active congestions. There is no use in here dwelling upon the symptoms of hepatic congestion which we shall find stated in a masterly manner by M. Chauffard in his work, nor upon the macroscopic appearances and the histological modifications of the organ in these cases. I will solely remind you of the sense of deep discomfort felt by the patient in the right hypochondrium, the painful tension with the pain radiating into the right shoulder; the increase in volume of the liver; its sensitiveness to palpation; the presence sometimes of an icteric tint of the conjunctivæ and of the skin; the presence in the urine of biliary pigments or

[1] Chauffard, *Traité de médecine*, de Charcot, Bouchard, Brissaud, t. iii., p. 778.

urobilin; albuminuria; alimentary glycosuria. All this is more or less temporary, ordinarily without fever, more or less pronounced, and repeating itself more or less frequently. I have not devoted my attention especially to cases of hepatic congestion, since the principal design of this work is to present the permanent form of enlarged liver of gastro-intestinal origin, which will be considered in the next chapter; I have not collected any observations of this kind, but it would however be easy for me to find a certain number of them, and every physician may be sure of running across similar livers. I saw some of them while I was an interne; I will only give a synopsis of the two following cases which concern persons whom I saw frequently and of which I have been able to follow the congestive periods.

Case xvii (personal).

Dr. X———, my colleague and friend, thirty years old. He is of gouty ancestry and is fairly stout (I do not dare to say that he is obese). He has never been seriously ill. Without being, properly speaking, dyspeptic, he frequently has trouble with his digestion, especially when he eats more heartily than usual; his epigastrium is distended, respiration is less easy, his face becomes red; it is impossible for him to work or even read for at least two hours, after meals. Several times both he and his colleagues have noticed a marked increase of volume of his liver, which then extends two, three, sometimes even four finger-breadths beyond the false ribs, and which returns more or less slowly to its normal volume, the next day or even two or three days after. At these times he experiences a feeling of tension in the right hypochondrium, but he has never had any icteric coloration, and has never noticed any biliary pigments or urobilin in his urine.

Case xviii (personal).

A young woman, twenty-six years old, whose very significant family antecedents I shall not mention, has had for some years past a great deal of trouble, which has exaggerated, out of all proportion, her natural nervousness, and made her, formerly a very cheerful person, almost a neurasthenic.

For a year she has suffered from quite severe pain in her stomach, especially when some time has elapsed since she has

eaten; the ingestion of food quiets this pain, which leads me to believe that she has a hyperpeptic form of gastric disease.

Her stomach, dilated and splashing, reaches to a finger-breadth above the umbilicus. Her liver extends two finger-breadths beyond the false ribs, and this condition is almost permanent; now and then its volume is even greater.[1]

[1] The same day as myself (July 19, 1894), Deguéret, my friend and colleague, presented to the faculty his thesis entitled, *Pathological Relations of the Liver and Stomach.* It was scarcely a month previously that we acquainted each other with the subjects of our theses. Save in regard to some details, our ideas were in perfect harmony. But our two memoirs, far from being duplicates, were rather complementary of each other. Deguéret has especially studied in their entirety the relations of the alimentary canal with the hepatic gland; he solely mentions, and as a probability, the gastro-intestinal origin of the cirrhoses. "In a great number of cases," says he, "anything which would remind us of alcoholism is lacking. . . . As to us, although our experience may be too limited to enable us to pronounce with certainty and to bring forward demonstrative facts in sufficient number, we believe that it is legitimate to consider the cirrhogenic action of gastro-intestinal disorders as infinitely probable. We know with what frequency hepatic disturbances supervene with dyspeptics."

From the point of view of hepatic congestion, Deguéret accepts the theory of M. Bouchard that: "Congestion of the liver is the consequence of a functional hyperactivity of the hepatic cell induced by the arrival in excess of toxins [it would be better to say poisons, for there are no toxins which come from the alimentary canal]. . . . The functional hyperactivity of the liver, supervening under these conditions, is comparable to the compensatory hypertrophy of the heart which Beau calls providential; to the abundant secretion of mucus by the glands of the gastric mucous membrane when it has to contend against the irritation of alcohol or a too acid gastric juice. . . . This glandular activity does not take place without a pronounced vaso-dilatation and a considerable afflux of blood. If this state of affairs is prolonged, the habitual hyperæmia entails its necessary consequences: cellular degeneration, irritation of the connective tissue, hyperplasia, cirrhosis. The functional disturbance has gradually led to the lesion. The hyperchlorhydria causes the gastritis and the atrophy of the mucous membrane; the prolonged irritation of the liver by the toxins leads to congestion, to degeneration and cirrhosis."

Deguéret distinguishes two forms or rather two processes of this hepatic congestion: *the congestion* of those subjects suffering from *dilatation of the stomach* with abnormal fermentations,—a *passive congestion* in which there is no acceleration of the course of the blood, but rather engorgement and stasis; and *the congestion of hypersthenic dyspeptics*,—this is almost constantly *active*, with exaggeration of the functional power of the organ.

In the first, we most frequently observe the signs of hepatic insufficiency; in the second, the absence of deposits of urates and of urobilinuria, the frequency of diarrhœa, a greenish color of the stools. His conclusions are explicit: "We believe that gastro-intestinal disorders have a considerable influence, if not the preponderant rôle, in the pathogeny of the cirrhoses of the liver. There is no doubt but that there are cirrhoses connected with gastro-intestinal disorders, as well with fermentative dyspepsias as with hypersthenic dyspepsias with hyperchlorhydria. Besides, every cause provocative of repeated and prolonged congestion of the liver, is susceptible of terminating in sclerosis of that organ." Deguéret would have had only to refer to the

The urine contains no urobilin, and but a small quantity of peptones. The urine has been examined but once. The complexion, formerly fresh and rosy, is now a dirty yellow, without, however, there being any icteric or urobilinic impregnation of the tissues. These two cases may be considered as benign. We shall see how far these congestive conditions may extend, and which frequently remain in this oscillatory, curable stage, but which sometimes terminate in confirmed cirrhosis.

communication made by M. Hanot and myself to the Congress held at Rome in the month of April, 1894, in order to see his conjectures surpassed by actual observation.

CHAPTER III.

CONFIRMED CIRRHOSIS OF THE LIVER OCCURRING IN THE COURSE OF DYSPEPSIAS.

In vain have I searched far and wide in medical literature for cases comparable to the following ones. As the majority of the clinicians who interest themselves in the study of diseases of the stomach have hitherto neglected to note the condition of the liver, not even indicating its volume, so also those who collect cases of affections of the liver only exceptionally pay any attention to the condition of the digestive functions, and very few, as we have seen, Budd, Leven, Bouchard, P. Le Gendre, R. Millon, considering that the liver and alimentary canal are parts of one and the same system, have studied the relations which unite the pathology of these three organs—stomach, liver, and intestinal canal.

At the present time a fresh current which is setting in this direction is attracting the attention of observers and this comparatively recent subject will soon be enriched by a goodly number of instructive cases. So far as cirrhosis is particularly concerned, after the publication of this thesis, it is to be hoped that we shall see reported cases similar to the following:

Case xix (personal).

Hereditary gout.—Nervousness.—Chronic dyspepsia.—Hyperpeptic gastritis.—Dilatation of the stomach.—Enlarged liver without icterus, without ascites, without collateral venous circulation, without enlargement of the spleen.—No alcoholism.

Madame J——, aged fifty-five years, is an innkeeper in the suburbs of Paris. We will at once remark that, notwithstanding her occupation, she has never drunk excessively, either wine or liquors. During her whole life, at each of her meals she has drunk two or three glasses of watered wine, and never drinks independently of her meals, except in summer when it is very

warm. Her *father*, who died at the age of seventy-four years, was also an innkeeper and was a hard drinker. He was dyspeptic for thirty years and was always rather particular about his food; for a long time he was in the habit of vomiting, especially during the latter years of his life.

Several times he vomited red blood. He was not stout, and was very much emaciated when he died, but had no ascites. Her father had two brothers and one sister, all three died at an advanced age, between seventy-eight and eighty years, never having been sick during their lives. Her *mother* died at seventy-four: she never drank anything except at her meals and never had tasted liqueurs. As long as the patient could remember, she always complained of her stomach.

For the last fifteen years of her life, she frequently vomited two or three hours after meals, not solid food but water; it was a true gastrorrhœa. She also suffered much from pain in the right hypochondrium, and her physician bled her for a disease of the liver; several times blisters were placed over the hepatic region. She was a robust woman. She had fifteen children, five died young and six others have since died: a son at thirty-five years, of a disease of the heart (angina pectoris?). Another son died at sixty-three years of age of an accident, and a third son at fifty, also the result of an accident in which he had some ribs broken. One daughter died at twenty-six years, after much trouble and sorrow; she sometimes slept forty-eight hours consecutively. Another son died at thirty-eight years of age of some disease of the stomach. The patient has no clear remembrance of the cause of the death of the sixth child. Four children are still living: a son sixty-five years old, stout and healthy, who has never suffered from his stomach; a daughter of sixty-eight years, who has been in Chili for thirty-five years, likewise healthy. Another daughter is a woman of fifty-seven years of age, who for many years has had trouble with her stomach.

Lastly, our patient, who is the thirteenth child, Madame J——, is a thin, lanky woman of medium height, very quick, intelligent, recounting her history perfectly. She had eruptions during infancy but no adenitis; she has not had any of the febrile diseases. When she was ten years old she had pleurisy, from which she soon recovered and from which she has experienced no ill effects. She menstruated at twelve years of age, and always normally until the menopause. Married between twenty-two and twenty-three

years of age, she has had six children: pregnancies and labors have been normal; last of all, during the war, she had a miscarriage at seven months as the result of a fall.

Until she was forty-three years old (twelve years ago), her health was perfect. However, her occupation of innkeeper necessitated some errors of diet, especially from the point of view of irregularity of meals. Twelve years ago, her indisposition commenced with an epigastric pain, at first dull, with some radiations to the left side, but especially to the right; at the same time the patient experienced extreme fatigue in her legs; she has some varicose veins.

This condition of affairs lasted about two years without the least vomiting. At the end of this period, the pain localized itself in the right hypochondrium, with a sensation of weight on the same side. At various intervals this pain became more severe, but without ever assuming the acute character of hepatic colic; no vomiting. After each of these periods of exacerbation, which lasted several days, her eyes were tinged with yellow, the urine became darker, the excretions were colored; this coloration (bile or simply urobilin?) lasted about a week. The patient was confined to her bed two or three days; her physician noticed the increase in size of the liver and applied a blister to the hepatic region.

For ten years past her appetite has been very capricious; sometimes good and sometimes bad. Digestion has always been painful and is accompanied three or four hours after meals by yawnings, by stretchings, by a sensation of weight in the epigastrium but no distension, eructations, or pyrosis. During the night her mouth is dry, her tongue foul, bitter; this condition is almost continuous. The patient is ordinarily constipated; she only has a passage once in two or three days; she never has any diarrhœa, except sometimes during the summer, when she eats fruit. Once after having been purged for three days with Rubinat water, calomel, and senna, there was over-purgation and diarrhœa for eight days.

For seven years her condition remained almost stationary with periods of aggravation. On the 29th of August, 1890, she consulted M. Hanot, who observed hypertrophy of the liver without jaundice, without increase in the size of the spleen, without ascites, and without increased venous abdominal circulation, and who prescribed the following: first, in the morning, a glass of milk;

second, at noon and at seven o'clock in the evening; to abstain from soups, stews, sauces, fats, starchy foods (except mashed potatoes with milk), acids, and raw fruits; to eat little bread; third, at each meal a glass of Pougues water with two spoonfuls of white wine; fourth, to take nothing between meals; fifth, before each meal to take one of the following powders: ℞ Naphthol *β*, magnesia, (āā) 0.30 for a powder; sixth, twice a week to take in the morning while fasting a soup-spoonful of Carlsbad salts dissolved in a glass of hot water. This treatment, carefully followed out, produced a marked improvement.

The patient came from time to time to have the cautery applied over her liver "when it was swollen," and she said she experienced great benefit from it, as she suffered at these times, and her eyes became yellow. Her digestion continued to improve. On the 6th of October, 1891, M. Hanot again saw the patient.

The liver was still enlarged. M. Hanot then added to the previous treatment 20 centigrams of calomel, to be taken twice a week in the morning before eating. January 31, 1894, we examined the patient. We gathered the preceding information and measured the *liver*. Superiorly this organ extends to the level of the fourth rib, and descends into the abdomen to about two finger-breadths from the crest of the ilium.

Upon the mammary line, it measures in height 25 centimetres, on the axillary line, 24 centimetres; it descends 15 centimetres below the xiphoid appendix, and extends towards the left hypochondrium 10 centimetres from the median line. Its free border, little removed from the crest of the ilium upon the axillary line, remains almost horizontally at this level as far as the vicinity of the umbilicus, above which it extends to the distance of two finger-breadths; it then takes a horizontal direction only to ascend and disappear under the left costal border at the union of its upper two-thirds with its inferior third. The border is uniform, rounded, but very perceptible, *very hard*. The surface of the remainder of the organ is also very hard, smooth, and without inequalities. Palpation is not painful. The *spleen* is not perceptible to percussion. The *abdomen* is not distended; there is no trace of ascites or any increased venous circulation.

The *stomach* is very much dilated; clapotage is clearly perceived, after ingestion of half a glass of water, at 5 centimetres below the umbilicus. Here are the results of the analysis of her

gastric juice made according to the method of Winter by M. Carrion, chief of the chemical laboratory of Professor Hayem.

Jan. 17, 1894.			*Results of the analysis.*	
Normal figures [1]			Hyper + Normal =	Hypo-
Total acidity	A	189	264	
Free HCl	H	44	168	
Combined HCl	C	168		135
Chlorhydria	H+C	212	303	
Total chlorine	T	321	467	
Fixed mineral chlorine	F	109	164	
Coefficient $\frac{A-H}{C}$		86		71

Peptones.....pure syntonin
Reactions of HCl.....observed
Residue.....colored
Fatty acids.....none
Small amount of liquid (12 c.c.) quite well emulsioned, mucous.

There is no *no icterus* nor any urobilinic coloration of the skin or conjunctivæ. The *urine* is of an amber-yellow color, contains no sugar, albumin, or urobilin. The urea was not estimated. Auscultation of the *heart* and *lungs* reveals no alteration of these organs; but there is dulness and diminution of the vesicular murmur in the lower third of the right lung; there are no pleural friction sounds.

The patient is very nervous, high-tempered; she has never had any nervous crises and presents no signs of hysteria. She belongs to a gouty family without herself presenting any other signs of this diathesis except some white hairs which commenced to appear when she was forty-five years old, and some hemorrhoids which only date back to the menopause.

Her sister, who lives in Chili, was gray at thirty, and the other sister has suffered from frequent attacks of migraine, very severe, with vomiting, which oblige her to keep her bed; she frequently also has epistaxis. The patient has a son who at twenty years of age already had some white hairs; he now is thirty-one, and his hair is quite gray. He also suffers from his stomach; after meals he almost constantly has a dull pain in his epigastrium and in his back between the shoulder-blades.

The patient, who has closely followed the prescribed diet, for

[1] All the numbers express milligrams.

the past eight days especially, feels much better from a gastric point of view. Occasionally only, about three or four o'clock in the afternoon, she has a little heaviness in her stomach and some yawning. In the evening she is tired and goes to bed quite early. She sleeps well during the first part of the night, but her sleep is lighter after one or two o'clock. She continually feels tired and cannot take any continuous exercise. We again saw the patient on the 13th of February. Mensuration of the liver gives us 24 centimetres only in the mammary line and 14 centimetres below the xiphoid appendix, or a centimetre less than the last mensuration.

The dyspeptic troubles are greatly improved; the patient eats and digests well; she experiences, after meals, no pain, no heaviness in the epigastrium. Her tongue is clean. The urine is normal; the hemorrhoids have not bled for six weeks. It seems that, in order to terminate in absolute hypertrophy, the liver of this woman has passed through a variable congestive phase in the course of which there have been some exacerbations. Having once attained its present size, the liver for several years past has remained stationary, manifesting solely at certain periods some slight differences, one or two centimetres more or less.

We cannot here see a simple chronic congestion; considering the remarkable hardness of the organ, it is with a true cirrhosis that we have to deal, and if none of the ordinary symptoms of the so-called alcoholic cirrhosis is present, it is undoubtedly because the distribution of the newly formed connective tissue does not sufficiently interfere with the portal circulation to produce ascites and to necessitate a collateral venous circulation.

But a time may come, if a medication, especially taking into consideration the condition of the alimentary canal, does not check the irritative process, of which the liver is the seat, in which the proliferation of connective tissue will be so great that ascites and an elargement of the superficial abdominal veins will manifest themselves. Case XXIV. will furnish us a remarkable example of it. The same considerations are applicable to the two following cases:

CASE XX (PERSONAL).

Gouty diathesis—Nervousness—Hemophilia—Dyspepsia since infancy—Dilatation of the stomach—Enlarged liver without icterus, collateral circulation, ascites, or enlargement of the Spleen—No alcoholism.

Madame B———, is forty-five years old. Her father, who died at the age of sixty, was obese and diabetic. Her mother, delicate and slender, died in childbed at thirty-four. Of three children, born of this household, one died young, another, a boy, is now a healthy adult; the patient is the third. Her health was delicate in childhood; she had scrofula, some cervical adenitis, and ciliary blepharitis. She menstruated at eleven years of age, and her menses have always been regular.

After marriage she only had one pregnancy, at nineteen, entirely normal. At thirty years, according to her statement, she had hepatic colic with vomiting, but without jaundice; this painful attack was of short duration. At thirty-five years of age she had meningitis (?) which lasted six weeks, without counting quite a long convalescence.

She has always been *very nervous*, without, however, having any nervous crises. She is lively, high-tempered, easily becomes angry, and is very impressionable. The news of the death of President Carnot (the patient came to see me on that day) affected her so greatly that she nearly lost consciousness, and for the whole day was trembling and weak; she had difficulty in standing erect. Very frequently she suffers from pains in the head, localized in the occiput. A year ago there was an increase in size of her thyroid gland. Professor Verneuil, who bled her at that time for menorrhagia, which we will consider farther on, several times injected the hypertrophied gland. At that time she did not notice that she had any trembling, palpitations, or exophthalmia, but she had some trembling before this epoch whenever she became emotional or angry; and since, she has some tachycardia when she walks a little too quickly or ascends a hill or a staircase; in connection with this she also sometimes has a slight sensation of retro-sternal anguish with a tendency to syncope.

She presents no *signs of hysteria.* Cutaneous sensation is rather exaggerated, but uniformly over the whole body. With her, the vaso-motor phenomena are remarkable: the least trau-

matism, a simple rap with the finger (*chiquenaude*), determines, at the contused point, a lasting redness, and even a slight ecchymosis which takes several days to absorb. From her earliest childhood she has had, up to twenty-five years of age, *frequent epistaxis*, which was repeated almost every day and lasted ten minutes.

Her brother, who, like her, has always easily bled from his nose, is yet to-day, at fifty years of age, subject to this accident, although very healthy. The menstrual flow of the patient has always been very abundant and lasts for eight days. During her pregnancy, there was a slight flow for the first four months. At the end of the sixth month there was also some flowing; during her confinement she lost a great deal of blood. Each sexual approach caused a slight hemorrhage, especially with her husband (she has been divorced some time and now lives with another man, less vigorous, she says). Since the beginning of March, 1894, she appears to have entered into the period of the menopause; she has had some severe hemorrhages, and has had to remain absolutely quiet; her strength has been very much diminished since this time. The physician who then attended her said that she had a *uterine fibroma;* but Professor Verneuil, who examined her uterus, found nothing abnormal. At the present time (May–June, 1894) her menses are very copious, and she has lost a little blood every day during the whole month of June.

I have, moreover, recently explored the uterus of this woman, and have found neither increase of size nor deviation of this organ. The *heart* beats normally and auscultation reveals no murmur, no abnormal sound. The *arteries* are neither hard nor tortuous. The pulse is very regular; the arterial tension, as well as it can be estimated without apparatus, seems normal. The patient is moderately obese; she has always been quite strong.

I have kept for the conclusion the history of the *digestive disturbances*. I at once remark that at no epoch has she drunk wine to excess; she scarcely takes even a glass of watered wine with her meals, and only very rarely takes a small quantity of liquor (a finger's-breadth in a small glass). Whenever she drinks any undiluted wine or alcoholic drinks it makes her digestion worse, already difficult. Between meals she has never taken, she asserts, and that only exceptionally, anything but pure water, beer, or syrups.

At all times this woman has had more or less distaste for food.

So to speak, she does not know the sensation of hunger; never has it happened to her to say: "Oh! how hungry I am!" Certain things do not digest well, and the patient carefully avoids eating such dishes, particularly fish, lobster, sauces, and fatty foods. Frequently after meals she has acid regurgitations and pyrosis. She has always been very constipated, only going to stool every two or three days, and then only after taking an enema. For ten years she has had trouble with her stomach, and her dyspepsia has grown worse during this period.

There is a sensation of weight in the epigastrium after meals; red blotches break out on her face, and there are patches of redness on the body, especially at the approach of her menses; at these periods, two or three hours after eating, vomiting takes place, not alimentary, but a clear and glairy fluid sometimes tinged with bile. For ten years she has also almost continuously experienced a feeling of weight in the right hypochondrium, which becomes more annoying a little before her menstrual periods.

At the moment her menses appear, to this feeling of oppression are added some painful sensations. Ordinarily she cannot lie on her right side on account of twinges of pain in this side. After she has lain down, if she suddenly rises and sits upon her buttocks, especially if at this time her right thigh is flexed upon her pelvis, she has a bruised, sore feeling in the right hypochondrium, followed for some time after by a dull pain.

Occasionally this pain radiates towards the right shoulder. Certain movements of the arms are always impossible, particularly their elevation above the level of the shoulders; the action of throwing a stone produces a sharp pain in the hepatic region. There has never been any *jaundice;* however, when she has her menses, her skin assumes a yellowish tint noticeable by her companions, and her urine becomes a little darker. I have seen this patient during and in the interval between her menstrual periods; I have been able to verify the absence of all abnormal coloration independently of the time of the menstrual flux, and, to the contrary, a very appreciable urobilinic impregnation of the conjunctivæ, scarcely visible in the skin, during the catamenial period.

The patient's urine was examined several times; it was light-colored, limpid, and plentiful. I have never found in it, even during the menstrual period, any albumin, sugar, biliary pigments, or urobilin. No test was made for alimentary glycosuria. The patient almost constantly has *itching*, as she expresses it, "between the flesh and the skin."

No eruption, no redness, she says, accounts for it. Tea provokes and exaggerates it in a remarkable manner. *Examination of the liver*, quite difficult on account of the corpulence of the patient, enables us, however, to exactly determine its size: it is markedly enlarged. We clearly perceive the inferior border at 11 centimetres below the edge of the false ribs. The organ is hard, *very hard*, resistant, smooth. Palpation is painful.

The dulness is perceptible in the mammary line as high as the third rib and extends to a little below the umbilicus. It measures: on the mammary line, 27 centimetres; on the xiphoid line, 18 centimetres; on the axillary line, 19 centimetres. Behind, the dulness commences at the inferior angle of the scapula. At this point we do not perceive any pleural friction sounds; neither were they perceived in the abdomen during auscultation of the hepatic region. There is *no splenic dulness, ascites, or collateral venous circulation on the abdomen.* The patient has some varicose veins and sometimes, but rarely, a little œdema of the legs. The *stomach* is greatly dilated. Percussion and clapotage enable us to trace its great curvature 21 centimetres below the xiphoid appendix, 3 centimetres below the umbilicus. The stomachal chemism was not studied. It was on the 13th of April, 1894, that I first thoroughly examined the patient and prescribed for her, co-incident with an appropriate diet, some powders containing each 30 centigrams of salol and as much bicarbonate of soda and calcined magnesia.

On the 30th of April she returned much improved; she has some appetite, she eats better, she no longer has any itching, she can lie on her right side. The liver is of the same size. She has only once had any pain in the right hypochondrium. The improvement was maintained until the 15th of June: at this time she had a severe attack of menorrhagia which very much weakened her. She left Paris June 30th in order to go into the country.

Of the two preceding cases, for the present I shall only speak of the very pronounced nervousness of these two patients. They would almost justify that phrase of Beau, perhaps more correct than at first sight it would appear: "All hysterical persons are necessarily dyspeptic." It is true that Beau's conception of hysteria was different from that of the present day: for him, hysteria was "a gastropathy with ascending dyspnœa, spasm of the glottis, and convulsions." Pathogenically at least, his idea of hysteria was different from ours.

CASE XXI (PERSONAL).

Gouty diathesis.—No alcoholism.—No apparent dyspepsia before the disease of the liver.—Dilatation of the stomach.—Enlarged liver without icterus, ascites, collateral circulation, or enlargement of the spleen.—Numerous hemorrhages in the course of the disease.

The said Rosalie N———, aged thirty-four years, charwoman, on the 27th of January, 1894, enters the service of Dr. Hanot at Saint Anthony Hospital. The hereditary antecedents are without interest. Her father, sixty-nine years old, is still living and healthy; he has never been ill.

Her mother died at fifty-nine of some undetermined affection. Neither parent was obese, dyspeptic, nor subject to migraine. Personally, this woman has always been comparatively healthy: no strumous antecedents in infancy, measles at six years, some paleness and anæmia from eleven to thirteen. Her menses, which appeared at fifteen years, have always been regular.

At eighteen years she had a normal pregnancy. At the age of twenty years she came to live in Paris, and two years after contracted typhoid fever. Starting from this time her health was excellent until she was thirty years old. At this time, after having taken cold during a menstrual period, her menses stopped and she had great lassitude and sharp pains in her lower extremities.

She entered La Pitié, where she remained six months. Upon her entrance they observed that her liver was enlarged and that she had some albumin in her urine; there was also a yellow tint of the integuments which soon disappeared, but no œdema of the lower extremities. This was four years ago. She left the hospital cured, but for two years and a half her menses did not reappear. She went to work, feeling quite well, coughing occasionally, catching cold very easily. Her hair had commenced to turn gray during her sojourn at La Pitié; at least, only then she perceived it. For a year past, without being obliged to keep her bed, without ceasing to work, her health is not so good: her strength is less, her appetite is diminishing. For six months her general condition has grown worse; the distaste which she experiences for food is accentuated daily.

In the first place she was not able to eat meat; then she could only take bouillon and milk. However, notwithstanding this

reduced alimentation, she does not grow thin: on the contrary, she says she is becoming stouter every day. For fifteen days past she can no longer even tolerate milk; she vomits it almost as soon as swallowed. In addition, her strength has diminished and she is obliged to abandon all work.

It is under these circumstances that she enters the hospital.

Condition of the patient in January, 1894.—She is an obese woman whose hair is almost gray: the integuments have a dirty yellow tinge, that of urobilin: the face is more tinged than the rest of the body, and the conjunctivæ still more. She preferably lies on her right side, listless; she slowly answers questions, as if with difficulty, plunged in a striking condition of apathy and indifference.

She complains of a cough, but says nothing of any localized pain. The tongue is a little foul, moist; no appetite; the disgust for food is unconquerable; milk even is rejected. The stools are quite regular, the excrements of normal color. There are no hemorrhoids. The liver is very large; its dulness ascends as far as the lower border of the fifth rib, and the lower limit descends in the mammary line to three finger-breadths below the umbilicus. It measures 27 centimetres in height. Between it and the median line, the dulness ascends almost vertically as far as the pit of the stomach, to redescend a little in the left hypochondrium. Palpation is not easy on account of the thickness of the panniculus adiposus; nevertheless we can reach the lower border of the organ, which is blunt, smooth, without sudden breaks; the surface also appears smooth.

It is of firm consistence, and the hand which has depressed the abdominal wall reaches a very resistant plane. There is no splenic dulness, no apparent abdominal venous circulation, save a lateral venule scarcely visible, and, moreover, frequent with normal individuals. No ascites. We do not perceive any stomachal clapotage; percussion limits the boundary of the stomach to about a finger-breadth above the umbilicus.

For seven years, but especially since her entrance to the hospital, the patient has spit blood: Is it hemoptysis, is it bleeding from the gums? It is difficult to decide; at one time the blood appearing in frothy strings; at another, almost free from admixture with the sputa. Auscultation of the chest does not solve the problem; sometimes we think we hear some subcrepitant râles at the apices, sometimes sibilant, sometimes nothing.

The heart presents nothing abnormal except a second aortic sound of a somewhat snapping character. The arteries are hard, slightly tortuous; the pulse beats eighty-four times a minute. There are no varicose veins, no œdema of the lower extremities. Since the beginning of her present illness, and perhaps a little before, the patient has had frequent attacks of epistaxis which occur almost every day. The urine contains urobilin in large amount; occasionally there is albumin; there is never any sugar or biliary pigments. April 8th, the patient left the hospital to resume her work, feeling quite well she said. She returned on the 12th, very feeble, without appetite, complaining of vertigo and headache. There were ecchymoses scattered over her whole body: back, chest, thighs, legs, forearms, and arms. There were two patches especially, as large as the palm of the hand, one on the anterior and the other on the posterior surface of the left arm.

In a few days, these ecchymoses passed through the whole gamut of tints and disappeared at the time other patches were appearing at different places. The epistaxis continued at various intervals. May 16th, there were still some ecchymoses, less numerous and especially less extensive than the preceding ones. Epistaxis is less frequent, but the patient still coughs and spits some blood, without the auscultation of the chest revealing any appreciable lesion. June 6th, the old ecchymoses having disappeared, some fresh ones took their places.

The patient constantly complains of weakness, of having headache and vertigo and of suffering from her stomach. For some days past she has had a slight hemorrhage from the vulva. For three days she has felt a slight pain in her right hypochondrium. Her liver, always very large, is sensitive to palpation and percussion. On the 9th of June, every hemorrhagic symptom had disappeared, and the patient, desirous of going to work, again left the hospital notwithstanding everything we said, but she came back again about the 15th, this time with a severe menorrhagia. By June 28th, the menorrhagia had ceased. At this time the patient was in a condition of extreme weakness and her face was of a pallor comparable to that of those rendered anæmic by traumatic hemorrhages; the lips and conjunctivæ were bloodless, the extremities constantly cold; the prostration was very pronounced. The dimensions of the liver have perceptibly diminished; the dulness in height only measures 21 centimetres. For the last time we examined the urine, which invariably con-

tained some albumin, a little indican, but no sugar, biliary pigments, or urobilin. Auscultation of the lungs, especially of the apices, gave the following results: resonance preserved, inspiration, a little gulping, expiration a little prolonged, equalling inspiration, and whistling during cough; no râles, no increased vocal resonance.

The history of Madame B——— and that of Rosalie N——— have a peculiarly interesting side, I refer to the severe hemorrhages manifesting themselves under different forms: with the first, dating from childhood; with the second, only going back seven years. This will be considered in the chapter upon etiology. Case XXI., in addition, has another complication: the continuous albuminuria from the beginning of her illness.

It would not be within the scope of this work to undertake a detailed investigation of the reciprocal relations of renal and hepatic affections, inasmuch as, perhaps, the true reason for the co-incidence of the two conditions might not be discovered. M. Bouchard, who has frequently observed either albuminuria or peptonuria with patients with enlarged livers, attributes these conditions to a defective functioning of the hepatic cell and recognizes an *hepatic albuminuria*, independent of every organic lesion of the kidneys, the liver being capable of causing proteid substances to undergo a modification which forces them to escape through the kidneys in the state of albumen. He has also observed albuminuria with individuals whose stomachs were dilated but whose livers were not enlarged, in a less proportion, it is true, than with those with whom the liver was congested, and, besides hepatic albuminuria, he recognizes a dyspeptic albuminuria. Nothing is more legitimate, and it is logical to think that the products of abnormal digestion which are, for the liver, a cause of congestion, and even of cirrhosis, may also have upon the kidney an injurious action inducing various lesions, simple congestion most frequently, sometimes confirmed sclerosis. We shall see farther on that a broader conception may connect together all these phenomena and unite, in the domain of the gouty diathesis, the gastric, hepatic, and renal manifestations of those people whose arteries and connective tissue are originally fragile.

Here are, although summarized, two cases of permanent enlargement of the liver with dyspeptics. They have been drawn up from the notes of M. Hanot who, at several times, has been able to see the patients.

CASE XXII (HANOT) UNPUBLISHED.

Dyspepsia.—No alcoholism.—Enlarged liver without icterus, ascites, collateral abdominal venous circulation, or enlargement of the spleen.

M. X———, physician practising in the provinces, came to see me in 1887. He is forty-five years old. For three years he has suffered from gastro-intestinal dyspepsia with incomplete anorexia. Digestion is painful and followed by acute and severe diarrhœa. His liver has been enlarged for a year, but there has been no ascites, icterus, or enlargement of the spleen; his liver is *very hard.*

The various physicians who have examined him have diagnosed his case as *hydatid cyst, cancer of the liver.* In 1887, I note an enlarged liver which descends to within two finger-breadths of the umbilicus; this organ is very hard, the surface and inferior border are smooth. There is no splenic dulness. The urine is entirely normal. The stomach is not dilated. At this particular time his dyspepsia was better and his general condition good. From 1887 until 1892, when I again examined the case, his liver remained the same although the dyspepsia had disappeared and the general condition was still good. Always absence of enlarged spleen, of icterus, of ascites, etc. Dr. X——— has always been a man of temperate habits.

CASE XXIII (HANOT) UNPUBLISHED.

Dyspepsia.—Dilatation of the stomach.—Large liver without icterus, ascites, or collateral venous circulation.—No enlargement of spleen.—No alcoholism.

M. X———, railway station-master, aged thirty-eight years, came to consult me, in 1888, for some dyspeptic troubles from which he had suffered for eighteen months. Digestion is painful but the patient has never vomited. The stomach is evidently dilated. He has never abused alcohol in any form. The liver reaches three finger-breadths beyond the costal border. No ascites, no subcutaneous abdominal veins, no splenic dulness, no icterus.

The urine contains neither sugar nor albumin. The patient

drinks little wine and no spirituous beverages. I saw him again in 1889. The dyspepsia has persisted. The liver now reaches six finger-breadths below the costal border. In 1890, a fresh exploration enabled me to note the stationary condition of the hepatic hypertrophy; the liver is still remarkably hard. The dyspepsia, however, is improved, for the treatment has been aimed in that direction. In 1892, I found the liver of the same size, always with absence of icterus, ascites, or appreciable enlargement of the spleen. The liver seemed to me harder than two years previously. The general condition is good. The urine is normal. The dyspeptic troubles have disappeared. Since this time, the health of the patient, from whom I hear occasionally, is excellent. I know nothing further in regard to the size of the liver.

Lastly, here is a sixth case, the sole one unfortunately in which there was a histological examination. It is the case of a patient whom MM. Millard and Hanot saw several times and whose history has been kindly communicated to me by Dr. Springer. It has been drawn up from some detailed notes furnished by him.

CASE XXIV (MILLARD-SPRINGER) UNPUBLISHED.

Gouty diathesis.—Gout.—Dyspepsia of long standing.—Enlarged liver without icterus, without splenic enlargement, and at first without ascites and collateral venous circulation; towards the end, marked ascites, dilatation of the abdominal veins.—Death.—Autopsy: sclerosis of all the portal and inter-trabecular spaces.

Madame C———, aged fifty-three years, presents nothing particular in her hereditary antecedents. Her father, a very active old man, is still living. Her pathological past only offers some temporary accidents; such as attacks of asthma with emphysema, which, moreover, completely disappeared two years ago. Some slight attacks of gout, soon quieted, came on four years ago, and no longer recur.

The psychological past of this patient, says Springer, who has intimately known her for a long time, has been strangely burdened. The life of this woman has been agitated and unfortunate; not that any violent sorrows or sudden catastrophes have affected her, but an uninterrupted series of annoyances, a life troublesome

and trying, had produced with her a condition of permanent irritation which manifested itself particularly at her meals; for at that time were gathered together those whom she accused of being the cause of her misfortunes. In July, 1890, the patient appeared to be in excellent health, having passed the change of life without accident, when she was suddenly taken with sharp pains in the right hypochondrium. The manner in which these pains appeared, their lancinating character, and their seat suggested hepatic colic.

Palpation of the liver revealed nothing abnormal (?). The patient soon went with her family to the seashore to pass the months of August and September. On her return to Paris she had no suffering and even had an excellent appetite; but her physiognomy had completely changed and her features were emaciated. On the other hand, her abdomen, which had always been large since her four pregnancies, appeared much more distended than formerly.

At this time we noticed a little ascites. All our attention was concentrated upon the liver. Its exploration was easy, owing to the emaciation and to the flexibility of the abdominal walls; it projected seven to eight centimetres beyond the costal border, covered the epigastric region and even extended into the left hypochondrium. Its edge was sharp and we could easily explore its inferior surface. This surface was hard, smooth, without any inequalities, and its consistence was uniform.

There was no increase of volume of the spleen. The stomach was not dilated. All the other organs appeared to be healthy. Dr. Millard, who then saw the patient, at first made the diagnosis of hepatic carcinoma, but with some reservations. During the whole month of October, 1890, her belly continued to swell, the ascites increased, and exploration became difficult. On November 16th, with the design of clearing up the diagnosis, the patient was tapped and two and a half litres of fluid removed. Exploration of the liver then revealed no change in its dimensions or characteristics. Although the patient had never had syphilis, the possibility of hepatic syphilis was considered and a specific treatment instituted. At the end of fifteen days there was no resulting improvement.

The belly constantly increasing in volume and venous dilatations manifesting themselves on the abdominal wall, we settled upon the diagnosis of cirrhosis without qualification. In fact,

there could be no question of alcoholism, the patient never having taken any spirituous liquors and never having drunk anything at her meals except wine diluted with water. Our information is precise in regard to this point. M. Hanot, called in consultation, gave the diagnosis of cancer of the liver. Commencing with the month of January, 1891, the patient rapidly grew weaker.

The digestive functions, however, were properly performed; the appetite was good, there was no distaste for food; the tongue was normally red. Diarrhœa was frequent. In order to mention everything which relates to the digestive passages, I must add that the patient having during the month of April taken some calomel pills (two centigrams daily), which produced a marked improvement in her general condition, there rapidly supervened an intense and very painful attack of stomatitis. In the early part of June the patient had thrush, which quickly yielded to treatment. Lastly, Springer lays stress upon the fact that the appetite and digestion were not impaired for a single moment, and that, up to the 16th of July, that is, a few days before her death, the patient took a sufficient amount of nourishment. The diarrhœa, however, was persistent. We never noticed any intestinal hemorrhage. During the course of the disease the patient was tapped several times. From November 16, 1890, to July 25, 1891, there were twenty-one tappings, by which one hundred and ninety litres of fluid were removed, or an average of nine litres per tapping. The hypertrophy of the liver remained stationary until May, 1891. At this time the liver seemed to diminish in size, to retract, while becoming of a firmer consistence. This retraction was very slow and little pronounced, for at the time of death, that is, two and a half months later, the liver had scarcely ascended two finger-breadths.

At this time the dulness extended to the splenic region, but it was difficult to say whether it was due to hypertrophy of the spleen or to development of the right lobe of the liver. The patient frequently complained of pains in this locality. In the course of January, the subcutaneous abdominal veins outlined themselves more plainly; the abdominal walls became the seat of a considerable œdema, which mended a little under the influence of diuretic treatment, but which soon increased and invaded the lower extremities; nevertheless the patient got up for an hour or two every day.

The urine was plentiful and never contained either sugar or

albumin. Save a temporary bronchitis contracted on the 10th of April as the result of a chill, the respiratory apparatus was always in good condition. There was no lesion of the heart. M. Hanot again visited the patient a few days before the end; the long duration of the affection appeared to him to justify his diagnosis of cancer of the liver; he refrained from making any other. The patient died July 25, 1891. The family did not permit a formal autopsy, only authorizing an incision in order to remove a portion of the liver. This operation was performed by Dr. Suchard, histological assistant to the College of France, who made the histological examination of the removed fragment. Here is the note which he sent to Dr. Springer:

"According to the directions which I had received, the liver alone was to be examined. Not being able to open the cadaver methodically, I made through the abdominal wall, in the median line and below the xiphoid appendix, an incision three centimetres in length. The anterior border of the liver appeared between the two lips of the incision, and, as well as I could judge by the introduction of my finger, this border appeared to me thickened and blunt. In the same way, I observed that the portions of the surface of the liver which I could touch were smooth and presented no elevations, no depressions.

"The parts of the stomach which I could draw near the incision by the aid of a tenaculum appeared normal. Acting then according to the instructions which had been given me, I removed from the anterior border of the liver a piece of that organ representing a volume of about two cubic centimetres. This fragment was yellow, bloodless; the surface of the liver forming one of its faces was smooth. Its consistency was almost elastic. Without difficulty my finger-nail penetrated the incised surface of the section.

"I noticed the same physical characteristics on the portions of the liver which I was able to explore by means of the finger introduced into the abdominal cavity. The incision was closed by some sutures. The fragment removed was divided so that some portions of it could be fixed by osmic acid, others by alcohol, and hardened by the successive action of picric acid, gum, and alcohol. Some sections were afterwards made of these portions of the liver. Those from the fragment hardened by picric acid, etc., were stained with picro-carminate of ammonia, and mounted in glycerine. Examined with a weak objective, we there remark

(Pl. I., Figs. 1 and 2): first, the integrity of the central vein of the lobule; second, the increase of extent of the portal spaces. With a strong objective, we easily discover that the central veins of the lobules are everywhere surrounded by normal hepatic cells; that these central veins themselves are not thickened; and, lastly, that the capillaries are empty in the vicinity of these central veins.

"If, with the same objective, we examine the portal spaces, we see that the connective tissue, which surrounds the portal vein and the biliary canals, is very much more abundant than in the normal condition, and that at certain points it invades the lobule by projecting itself around the compressed biliary canals, and spreading, so to speak, between the intervals of the hepatic cells.

"The portal veins of the portal spaces contain red and white blood globules. A great number of these elements were scattered, by means of diapedesis, through the connective tissue of the portal spaces, being located between the bundles of connective tissue. The inflammatory lesions of this tissue are remarkable, and appear generalized in all the portal spaces which I have examined. They are characterized by the presence of numerous white globules and swelling of the nuclei of the fixed tissue cells.

"Moreover, at no point do we remark any collection of embryonic cells sufficient to form an abscess or to characterize a syphilitic gumma of the liver. In the preparations obtained by section, after fixation of the tissues by osmic acid, and examined in water with a strong objective, we remark, independently of the normal condition of the hepatic cells of the centre of the lobule, the fatty surcharge of a certain number of the peripheral cells of the lobules, and granular fatty degeneration of some cells in the vicinity of the portal spaces. Iodine solution and Paris violet indicate no amyloid degeneration, either in the sections made before the addition of any reagent, or in the sections made after hardening of the tissues by the processes above mentioned. These lesions being discovered, the anatomical diagnosis is evidently that of hypertrophic cirrhosis.

"This cirrhosis is characterized by chronic lesions (increase of the amount of connective tissue of the portal spaces) and by acute lesions (acute inflammation of this tissue). The fatty degeneration which is the termination of the majority of cases of cirrhosis

is not yet very far advanced in the fragment examined; but nevertheless it is present. The cause of this hepatic cirrhosis cannot be determined by the examination of so small a portion of the liver, the condition of the other organs being unknown."

Case xxv (unpublished).

Towards the end of 1894, Dr. Levillain (of Nice) sent to M. Hanot a patient, the bearer of the following note: "M. G——, fifty-two years old. Mining superintendent. Father had sciatica; sister dead, rachitic. M. G——. Infancy: rachitic deformities; bowed legs. At seven years of age operation for stone: then good general health; at fifteen, jaundice, consequent upon emotion; at twenty-five, attack of appendicitis; at twenty-nine, another attack of jaundice; at forty-six, nephritic colic for three days; at forty-eight, itching in the perinæum, dull colics in the lower belly, vesical tenesmus, and expulsion of gravel. For a long time, gastric disorders, stomach always delicate. For the last three or four years especially, these troubles are more complained of (distaste for meat, odors of the kitchen disagreeable and spoiling the appetite); progressive aggravation of the dyspeptic phenomena (distension of the stomach, gas and eructations after meals), pain in the gastro-hepatic region, which is sensitive to pressure and presents a very marked dulness.

In addition, and probably as a result of these gastric disturbances: development of a slight secondary neurasthenic condition (pains in the head with attacks of headache and painful points), insomnia, and matutinal amyosthenia, clearly coinciding with the stomach troubles; psychical asthenia, work more difficult, memory impaired, urine with coefficient of insufficient utilization with traces of biliary pigment.

M. G———, before consultation, went to Royat, and took a slight course of thermal treatment. Some gastric disturbances have come on which have led me to advise him to abandon this treatment, and I have persuaded him to seek counsel and have his abdominal viscera examined, and particularly his gastro-hepatic region. Dr. Hanot saw the patient, and observed a considerable increase of the size of the liver, without icterus, ascites, increase of circulation, or enlargement of the spleen. In consideration of these facts and a remarkable hardness of the organ, he has not hesitated to give the diagnosis of "dyspeptic cirrhosis."

Here are found united: congenital malformation (rachitis), gouty diathesis (precocious renal lithiasis, constant digestive disturbances), hepatic weakness (two attacks of icterus without well determined cause). The soil was well prepared for the development of a cirrhosis under the influence of noxious substances elaborated in a diseased alimentary canal.

In order to condense in a comprehensive table *the symptoms of non-alcoholic cirrhosis of the liver, caused by auto-intoxication of gastro-intestinal origin*, I will reproduce in part the note presented by M. Hanot and myself to the Congress at Rome. With adults of thirty-five to fifty-five years of age we find, at the acme of the disease, an enlarged liver projecting four to eight finger-breadths beyond the false ribs, measuring 20 to 25 centimetres in height on the mammary line.

Its surface is uniform, smooth, without indentations or protuberances; the edge is readily perceptible, although a little thickened. *This organ is remarkably hard; we may even say that it is almost as hard as wood.* This is its most striking characteristic. Palpation is not at all or only slightly painful. There is no appreciable increase of the size of the spleen; for a long time no ascites, no increase of the collateral abdominal venous circulation; never any icterus, but an urobilinic coloration of the integuments which may also be lacking.

Most frequently the urine is normal, it however may contain some urobilin and sometimes more or less albumin; we have never found any sugar. If we interrogate the patients, we find no history of alcoholism (our observations are precise in regard to this point), neither do we find any tuberculosis, impaludism, syphilis, or any apparent cause of old or recent infection. But we ascertain that for many years the patients have been dyspeptic, either constantly or intermittently, with or without dilatation of the stomach. With the patients whom we have had under observation for some time, we have seen the liver gradually increasing in size, this organ only slowly attaining the dimensions above mentioned. But at the beginning, the liver had this same woody hardness, perhaps a little less pronounced in the first place. When the liver has attained a certain degree of hypertrophy, this organ remains almost stationary, and this for a very long time; two of our patients were under observation for seven years. Functional troubles are complained of but little. Independent of the dyspepsia, which is persistent, save thera-

peutic intervention, we notice only a sensation of weight in the right hypochrondrium, some tympanites, habitual constipation, and a certain lassitude which renders manual labor more difficult and more quickly fatiguing.

However, the patients are also subject to some acute accidents, ordinarily temporary, and consisting in bilious attacks (embarras gastriques) during which the liver slightly increases in size, and at the same time some urobilin appears in the urine. The patients may also have more or less intense attacks of perihepatitis which remind us of aborted hepatic colic. The termination appears to take place, if we can judge of it by the only fatal case observed, by an exaggeration of the cirrhotic process and the mechanism habitual to the so-called alcoholic scleroses of the liver.

Possibly profuse hemorrhages, like those of Case XX., might induce a fatal termination. We can then say that the prognosis *quoad vitam* of such an affection is rather favorable, taking into account, however, the possibility of hemorrhages and of a rapid increase of the proliferation of connective tissue.

In addition, such a liver is more susceptible than another to intercurrent affections, and, as with all the cirrhoses, the prognosis is governed by the condition of the hepatic cell. *Can there be an atrophic cirrhosis resulting from auto-intoxication of gastro-intestinal origin?* Under the title of "A Case of Hepatic Cirrhosis with Hemorrhages from the Dilated Submucous Æsophageal Veins," there has been published by M. Kutreff[1] the following case:

CASE XXVI (KUTREFF).

Merchant, aged sixty-five years. Suffered for many years from a periodical flux of gastric juice. Violent hematemesis. Rather stout and robust. Dilatation of the heart. Slight arterio-sclerosis. Quite pale. Slight jaundice. Abdomen enlarged. Constipation. After a few days: dryness of the tongue, insomnia, general critical condition.

In consequence of large rectal enemas: improvement. Relapse. Distension of the abdomen. Hepatic dulness much lessened, that of the spleen not increased; no sign of ascites. The urine contained neither albumin, sugar, nor biliary coloring mat-

[1] N. Kutreff, *Eira*, xxxviii, 15, pp. 469–475. Analysé par A. F. Eklund in *Revue internat. de médecine et de chirurg, pratiques*, September 25, 1894.

ters. Again improvement as a result of same treatment more energetic. Second relapse, with hematemesis. Chills, slight fever, with sweating. By palpation large masses of solid fæces could be detected in the sigmoid flexure. Sweetish and sickening odor of the breath.

Agitated and delirious; spasmodic movements of the arms and legs. Fatal termination. Autopsy: Above the cardia the œsophagus was everywhere filled with true submucous varices, quite large and a little tortuous. The transverse colon was so large that it occupied the whole territory between the ensiform appendix and the umbilicus.

No ulcer of the stomach, no cicatrix. Common hepatic cirrhosis *as a result of the action of noxious products of decomposition in the intestinal canal.* The abuse of alcohol, intermittent fever, and syphilis may be excluded as etiological factors. The febrile condition and the cerebral symptoms were due to the auto-intoxication from the alimentary canal.

I give this case without commentary as I have not been able to see the original work, but it affords matter for many reflections which we would attempt to formulate if we did not fear to run counter to sacred dogmas; some of them, however, will be hazarded a little later, when experiments have shown what abnormal products are capable of doing, acids especially, when elaborated in a diseased intestinal canal.[1]

[1] Without speaking of the cases of infantile cirrhosis in the production of which the action of alcohol cannot be invoked and which are probably caused by infection, we must consider those cases of cirrhosis not caused by alcohol and of which the etiology is unknown.

If we wished to force matters, we might suspect the gastro-intestinal origin of the very interesting cases collected by Lafitte in his thesis, although he does not especially make mention of anterior digestive disturbances. It is much better to leave the pathogeny of these cases uncertain than to run the risk of being suspected of making the facts conform to the system.

CHAPTER IV.

ETIOLOGY AND PATHOGENY.

THAT which perhaps some minds will admit with difficulty, is that the affection of the liver of which we have just seen the two forms, congestion and cirrhosis, is undoubtedly connected with the bad condition of the digestive passages and finds its sufficient reason in an auto-intoxication of gastro-intestinal origin. The first portion of this work, devoted to the study of the poisons of the alimentary canal, is, however, of a kind, it would seem, to induce conviction.

In order still further to support this etiology, I shall invoke the aid of a successful experimentation, the details of which will be found in the third portion of this work. But there are some objections to which I must respond. Consider, they will say to me, the large number of dyspeptics whom we encounter and the small number whose livers are diseased.

Consider also that the poisons of which you speak can be found in almost equal amounts in everybody, and that the liver by means of increased activity, little harassing, can transform and destroy them ; lastly, you have only seven cases of this so-called cirrhosis and only one autopsy and that incomplete.

I will say, in the first place, that in the past we have not sufficiently investigated and do not now sufficiently investigate the condition of the liver in diseases of the stomach, and that future statistics, taking into consideration this fact, and not accepting solely as capable of fabricating gastro-intestinal poisons, those persons whose stomachs are manifestly dilated, will show with dyspeptics a much larger proportion of livers at least congested.

I will next say that, if we are more or less well acquainted with the list of poisons which may originate in the alimentary canal, we are almost completely ignorant in regard to the quantity in which they are produced, and especially we are only very imperfectly informed in regard to their noxious effects so far as the liver is concerned.

There is here a coefficient which it is all but impossible to determine, especially if we take into consideration the principal factor, the individual affected by the auto-intoxication. As with infection, the question of a suitable terrain here takes precedence of every other pathogenic condition. We must confess that each one of us has a manner peculiar to himself in the way in which he resists the attacks of autochthonous poisons, and that the hepatic cells as well as the vessels of the liver have in this respect a greater or less susceptibility.

Do we not see certain articles of food well tolerated by one stomach which will produce indigestion in another, a true intoxication even? An example which I borrow from Chomel shows the reality of this fact of common observation. "Gamy meats, so sought after by gourmets, even those which are only slightly touched, are poisonous for some persons. With these individuals, the ingestion of such meats is promptly followed by expulsion of fæcal matters of an excessive fetidity recalling that of decomposed flesh. What is peculiarly remarkable is that their quantity all but equals that of the ingested poisonous food. Other foods taken at the same meal are retained and well digested; and frequently the stool of the next day is entirely normal."[1]

On the other hand, a goodly number of people ingest no matter what gamy meats without being incommoded, even several days in succession or habitually. This is what for a long time has been called *idiosyncrasy*. That which takes place in the stomach or intestine may equally take place in the liver; and, as the gastro-intestinal canal shows a greater or less susceptibility, so the liver may show itself, relatively to the poisons which the afferent vein brings to it, more or less delicate, more or less vulnerable.

It is probable that the hepatic cell, one of the functions of which is the transformation of poisons, bears to this task a greater or less capacity, a greater or less efficiency. One liver will not transform many a poison; another "fears none." Thus there are some stomachs which the least error in diet renders unfit for the performance of their digestive functions; others "which can digest stones."

Then supposing that all dyspepsias resemble each other, that in all we find the same products of abnormal digestion, that in every intestine one and the same sum of fermentation and of

[1] Chomel, *Des dyspepsies*, 1857, page 30.

microbian toxins can be proven, it will not remain the less true that this figure x of abnormal and poisonous irritant products will find a liver of vascular resistance, of cellular function, varying with the individual.

The question, very general, moreover, is here found closely brought home. Is there a reason for this *hepatic idiosyncrasy?* Yes, certainly, and I will say that it is easier to find than that of gastro-intestinal idiosyncrasy. We might incriminate a defective equilibrium of the nervous system, an innervation more or less defective of the organ, as we invoke for the stomach some reflexes too readily put in action by many articles of food. In fact there may be a *nervous dyshepatia* as well as a *nervous dyspepsia*, and besides, *imbecillitas ventriculi*, *imbecillitas jecoris*. I believe with my master Hanot, that the cause is more profound, more organic, if we may say so, especially when it is a question of this special vulnerability of the vasculo-connective portion of the organ, and that we may here boldly invoke the gouty diathesis (arthritism).

In a very learned and much noticed lecture, M. Hanot[1] endeavors to show the importance of predisposition in the production of hepatic cirrhosis in general, which he defines "as an affection for which the gouty diathesis paves the way; which is determined by an intoxication and terminated by an infection: the diathesis rendering easier the intoxication and the intoxication rendering easier the final infection."

In fact, in *all* the cases of cirrhosis, nascent or confirmed, in the practice of M. Hanot during the year 1893—a little more than a dozen, while only counting the so-called alcoholic cirrhoses—we have found the gouty diathesis as the predisposing cause. We may read a detailed account of these cases in the excellent thesis of Dr. A. Le Roux,[2] who has brilliantly developed the ideas of our master from this point of view.

Of seven cases of cirrhosis which I present, five only relate the hereditary and personal antecedents of the patients, and four of them have as a heading the words "gouty diathesis." The father of the first patient (Case XIX) was dyspeptic for thirty years; her mother always suffered from her stomach, and had a disease of the liver. Of fifteen children that they had, five died

[1] Hanot, "Consid. gén. sur la cirrhose alcohol." *Sem. médicale*, p. 209.

[2] A. Le Roux, "Contrib. à l'étude de la cirrhose hepat. alcoholique. Prédisposition et précirrhose." *Thèse de Paris*, 1894.

young, another of angina pectoris; the patient herself, very nervous, was dyspeptic for many years, and has gray hair and hemorrhoids. Her sister has very frequently had epistaxis, and has suffered from frequent attacks of migraine. The son of this patient had gray hair at twenty years of age, and has also suffered from his stomach.

The second woman (Case XX) is the issue of an obese and diabetic father; she is very nervous, a hemophile, as well as one of her brothers; she is dyspeptic since childhood. The third woman (Case XXI) has, so to speak, no history; she is the only hospital patient whom we have had under observation. However, she is obese, emphysematous, and has had gray hair for some years.

The fourth (Case XXIV) was gouty, emphysematous, and asthmatic. In the case of Levillain (Case XXV), the gouty diathesis was manifested by precocious renal lithiasis and constant digestive disturbances. Lastly, in the case of Kutreff (Case XXVI), the patient was obese, and had arterio-sclerosis.

I do not speak of the two cases of congestion of the liver which I have reported; there also the gouty diathesis is the key to these morbid manifestations. What must we understand by the gouty diathesis, and what relation has this constitutional condition to hepatic cirrhosis and to sclerotic processes in general? I do not wish to enter upon this extensive and serious question, which M. Hanot and his pupil Le Roux have studied with all the development which it admits of; I will only quote, since everyone is now agreed in regard to the manifestations of this "morbid temperament" (Bouchard), the definition of my master: "The gouty diathesis is a constitutional condition characterized, among other constituent elements, by a vitiation, ordinarily congenital and hereditary, of the connective tissue and its derivatives, which become tissues of least resistance." M. Hanot adds: "These congenital malformations of a whole system abound in general pathology: congenital debility of the cardio-vascular system of chlorotics, of the nervous system with the hysterical and degenerate, of the pulmonary apparatus (emphysema and thoracic malformations) with those predisposed to tuberculosis, etc."

Placing himself at a morphological point of view, M. Hanot, with the embryo, very logically recognizes a defect in the constitution of the middle layer of the blastoderm, the layer from whence connective tissue and its derivatives originate. This

alteration may be encountered independent of heredity, in arthritic children born of parents free from this diathesis, but physiologically debilitated by infection or intoxication: saturnism, alcoholism, morphinomania, tuberculosis, syphilis, etc.; so many causes influencing the development of the embryo,[1] arresting it either in its total evolution or in that of one of its parts; affecting sometimes the external layer, of which the malformation will be revealed by tremendous disturbances of the nervous system, sometimes the middle layer, and thus giving rise to arthritics (Le Roux). "From a functional and anatomo-pathological point of view," again says M. Hanot, "the gouty diathesis is characterized by an excessive vulnerability of the connective tissue, with a tendency to hyperplasia, to fibrous transformation, to fibrous contraction." We find the same idea expressed in almost the same terms in a monograph of Dr. Cazalis[2]: "There is with arthritics a predisposition of the connective tissue, undoubtedly consequent upon some defect, to a special irritability which, in the organism, makes of it a place of least resistance, or a place of election for the diseases of the gouty diathesis, whence, with these patients, the so frequent inflammations and proliferations of this tissue . . . The question of the gouty diathesis would then be, above everything else, a question of morphology, and we will easily thus comprehend the heredity of the diathesis."

Fortified with these data, we can comprehend why arthritics alone have cirrhosis. In fact, it is permissible to suppose that, with arthritics, the connective tissue of the liver, as well as the vascular venous walls, will be intensely and profoundly modified by irritating substances which, in the case of other individuals, would leave the organ intact.

"There is no disease," says Cazalis, "without a predisposition of the organ to the disease which affects it. All alcoholics, all syphilitics, do not have sclerosis of the liver or spinal cord, and we believe that, with many of these scleroses, we would find the gouty diathesis if we thought of looking for it."

Le Roux very judiciously makes the remark that frequently

[1] See the report of the experiments, full of interest, which M. Féré communicated this year to the Bacteriological Society in regard to the production of malformations of the embryo of the chick, by the introduction into the egg of chemical poisonous substances and toxins.

[2] A. Cazalis (d'Aix-les-Bains), *Hygiène et régime des arthritiq.* Paris, 1891.

the individual who becomes cirrhotic, presents the minimum of the signs of the gouty diathesis, the same also as he presents the minimum of the signs of alcoholism. It seems that the diathesis, as well as the intoxication, has had for the liver a predilection, disdaining to attack other portions of the organism. To support this pathogenic conception of cirrhosis of the liver, I will call to mind the recent communication of Professor Verneuil to the Academy of Medicine.[1]

This eminent mind has been struck by the connection which exists between the gouty diathesis, fragility of the arteries, and disease of the liver. It is true that he otherwise interprets the relations of these morbid conditions, and that he gives to the *hepatism* the preponderant rôle in the production of hemorrhages, even of the epistaxis of infancy and youth. This is the doctrine which M. Glénard of Lyons has resurrected from the enthusiastic memoir of Poucel. "The hepatic lesion," says this author (p. 14), "is the cause of the arthritic diathesis."

And farther on (p. 104): "It being admitted, according to us, that the congestion of the liver is sometimes the *cause* and sometimes the *condition of every disease*, it is important to state if there is a constant connection between the condition of this organ and the diathesis which causes the morbid predispositions. This connection is unquestionable, and we have observed in a general manner that the maximum increase of volume of the liver corresponds to the rheumatism, to the gout, to the lithiasis, to the diabetes, and that its reduction takes place during the consumptive period of these various conditions. We add that *they die of arthritic consumption entirely the same as they die of scrofulous consumption.*" This, it seems to me, is taking the effect for the cause. It makes little difference. I merely call to mind the fact that two of my patients (Cases XX and XXI) have had a tendency to hemorrhage: one, since her infancy (and that at the same time as her brother); the other, three years before the confirmed disease of the liver.

This question of hemorrhages in cirrhoses is treated by another pupil of M. Hanot, Dr. Octave Bossu, whose thesis will appear at the same time as mine, and in which will be again found my two cases. In a monograph upon "The Etiology of the Vascular Cirrhoses of the Liver," Dr. Kabanoff,[2] physician of the clinic of Prof.

[1] Verneuil, Académie de médecine. Séance du 29 mai, 1894.

[2] N. Kabanoff, *Archives générales de médecine*, février et mars, 1895.

Ostrooumoff of Moscow, mentions all the sclerotic processes which he has encountered with fourteen cirrhotic individuals: sclerosis of the skin, lungs, myocardium, endocardium, blood-vessels, kidneys, peritonæum, pleura, and gastro-intestinal canal.

He also mentions epistaxis and hemorrhoidal bleeding as manifesting themselves a long while before the cirrhosis of the liver. For him, this cirrhosis cannot be considered as an independent and autonomous disease, as a morbid entity, but as a part of the disease of the whole organism. He invokes hereditary or congenital predisposition, the majority of his patients presenting some defect or malformation which made them true degenerates. Some passages of this monograph merit quotation.

"In order that a disease be produced by external agents, it is necessary that these act with great intensity (violent poisons, traumatisms, etc.). It is then essential that something else aids the external action, and this thing is the *predisposition* of the organ or organism: it is the *internal etiology*. It is certain that, as yet, we know relatively but little in regard to the functioning of the liver, much less than in regard to other organs; also we can judge only very imperfectly of the small deviations which it may have presented in the patient's past, variations and changes which precisely determine by themselves the predisposition, the receptivity favoring the development of the disease.

"We must, moreover, consider that the predisposition is rarely confined to one organ, all the others remaining absolutely sound. Ordinarily it is the entire organism which is in a condition of greater or less vulnerability; the vital activity is everywhere diminished, metabolism is modified and disordered. However, all the organs do not participate in these disturbances in the same proportions: one organ may to a high degree present this predisposition, another will scarcely feel the effects of it.

"It is easy to notice, in fact, that rarely is a single organ diseased. With a patient affected with cirrhosis it is extremely seldom that we find only the liver affected; several other organs ordinarily participate more or less in the pathological condition. In no case does cirrhosis of the liver appear to us as an independent and individualized disease, but as a part of a disease of the whole organism, and constitutes, so to speak, a complicated symptom, a syndrome in the general affection."

The conclusions of M. Kabanoff are, first: "that the more

strongly the weakness of organization is expressed (hereditary or congenital), the more profound is the degree of degeneration, the sooner commence the pathological disturbances, and the more considerable they are; and in such a terrain very slight causes may provoke grave lesions. Secondly, with a considerable congenital weakness on the part of the liver, a weakness which, in the majority of cases, if not in all, coincides with a greater or less weakness of the whole organism, the cirrhotic process may be provoked by any external cause, however insignificant."

Thus in the rôle which the gouty diathesis plays in the pathogeny of cirrhosis, it is a question above everything else of the natural fragility of the vessels of the liver. The other vessels are not protected from injury, and atheroma is the heritage of the gouty diathesis. The kidneys do not escape vascular sclerosis which sometimes develops without appreciable cause; with so much the more reason if a diseased liver permits irritant products to reach them, either because it has not retained or transformed them, or because it has elaborated some of them itself, its function being perverted.

We comprehend, therefore, that the lesion of the two organs may be united, and that the pathological condition of the one may react fatally upon the other. I have already spoken of the nervousness of two of my patients (Cases XVIII and XIX). This evidence would besides show, if there were any necessity for it, the close bond which unites the malformation of the nervous cell with that of the vasculo-connective cell, that which Charcot has so happily expressed by the term *neuro-arthritism.*

Fig. 1.

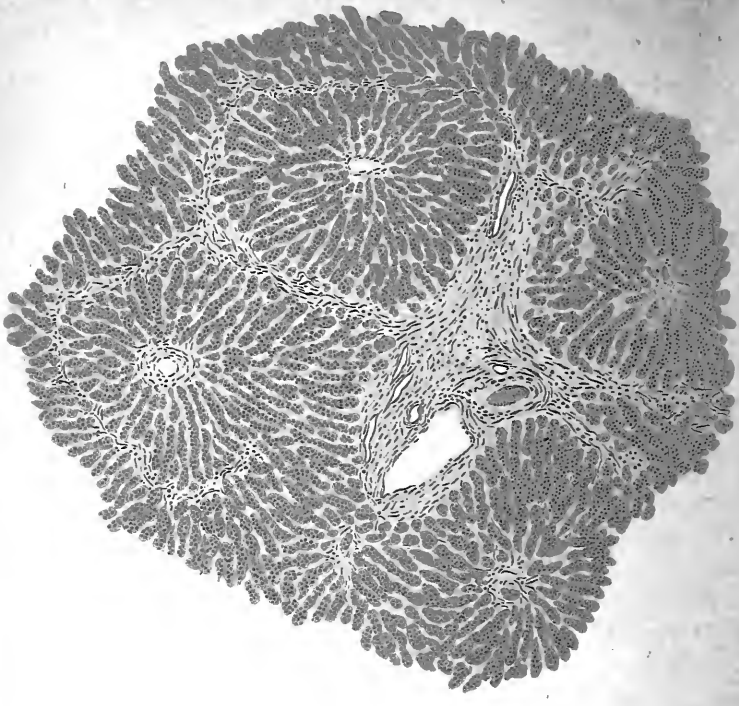
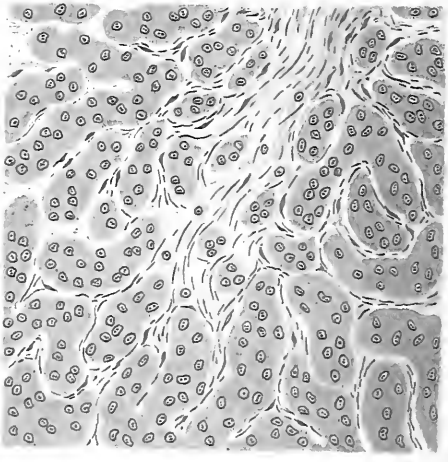


Fig. 2.



Gillet del. Imp. Lemercier, Paris. Nicolet lith.

PLATE I

Fig. 1 (Leitz, oc. 1, objec. 4).

Peri-portal and intra-lobular sclerosis, with mono-cellular tendency. The [illegible] of the lobule is also perceptibly sclerosed. The figure does not show [illegible] fatty degeneration of the lobule, entirely marginal.

Fig. 2 (Leitz, oc. 1, objec. 7).

A portion of Figure 1 has been specially enlarged in order to show the endo-inflammation and the penetration of the connective tissue between [illegible]

PLATE I.

FIG. 1 (Leitz, oc. 1, objec. 4).

...-portal and intra-lobular sclerosis, with mono-nu... ...
... of the lobule is also perceptibly sclerosed. ... ...
... of fatty degeneration of the lobule, entirely marginal.

FIG. 2 (Leitz, oc. 1, objec. 7).

A point of Figure 1 has been greatly enlarged in order to sh... ... ...
... inflammation and the penetration of the connective tissue ... ...
... shades.

FIG. 2.

CHAPTER V.

PATHOLOGICAL ANATOMY OF DYSPEPTIC CIRRHOSIS AND ITS PLACE AMONG THE CIRRHOSES OF THE LIVER.

In Case XXIV we have seen the result of the histological examination made by M. Suchard. Through his kindness I have been able to obtain a fragment of this liver which I have cut into sections and stained with the reagents ordinarily employed: picrocarmin, hematoxylin, and eosin. I have made the same discoveries as M. Suchard, but I will, nevertheless, here dwell upon some points. (Pl. I, Figs. 1 and 2.)

The sclerosis of the porto-biliary spaces is generalized; it has no tendency to form very large masses; it contents itself sometimes with thickening very markedly the areolar tissue spaces, and only does it *en passant*, so to speak, for it soon invades the interior of the lobule. In fact, the edges of these portal plaques, far from being sharply defined by normally arranged hepatic cells, are sinuous, slashed, and send to the interior of the lobules a very great number of ramifications.

If in some portal spaces the classic triangular form is still preserved, in the majority of them it is unrecognizable on account of the insertion in their borders of numerous intra-lobular connective-tissue tracts. In the sections, we quite frequently encounter fibrous lines which unite two or even several portal spaces; at some points the lobules are thus almost entirely surrounded by a ring of connective tissue. In these portal spaces we do not observe any new canalicular formation. In some, the sclerosis is so great that the lumen of the interlobular vein has completely disappeared through endoarteritis.

This endoarteritis is continued along the portal capillaries, in such a manner that some fibrous trabeculæ, quite thick sometimes, penetrate between the rows of hepatic cells, the pericapillary inflammation no longer permitting their junction with the cellular spaces. These, although sufficiently respected in

their arrangement, are disassociated and even frequently sinuous and distorted.

This condition does not reach to the extent of their disposition in a whorl, which we see in certain forms of syphilitic sclerosis. In the vicinity of the portal spaces we encounter some cellular groups completely encompassed by fibrous tissue. The central vein of the lobule, unaffected in some lobules, in others is markedly thickened; as for the portal space, we see starting from its circumference and at certain points only, lines of connective tissue which insinuate themselves between the cells in the direction of the radius of the lobule and also interrupt the cellular spaces.

So that, in certain lobules there is really, by virtue of the consensus of the bi-venous sclerosis, a true monocellular cirrhosis. The fatty degeneration of the cells is of but small moment. It is more markedly observed at the periphery of certain lobules, close to the portal spaces, reminding us of that which Sabourin has described under the name of fatty nodular cirrhosis; but in many of the lobules the cells are unaffected. *Upon the whole*, it is a question of a *diffused generalized interstitial hepatitis with monocellular tendency.* From a macroscopic point of view, we only know that the liver was large, smooth, and elastic. We are struck with the analogy which such alterations present with those of the liver of certain tuberculous alcoholics, which have been described under the name of *fatty hypertrophic cirrhosis.* There is only lacking here the more generalized steatosis. Such has been the reflection of M. Sabourin, who has been kind enough to examine my preparations. I borrow from the thesis of Bouygues the histological description of this cirrhosis investigated in the first place simultaneously by Hutinel and Sabourin, then by Gilson, Bellangé, Hanot and Lauth, etc.

"The tissue is strewn with irregular fibrous bands describing a rounded course and appearing to form complete rings. Sometimes a true annular cirrhosis is formed, but most frequently the rings are incomplete and terminate by radiating into the interval between the hepatic cells. The sclerosis presents its maximum of thickness at the level of the portal spaces; it is there that it seems to have commenced, and by referring to the forms we have studied, we see that it is there that we find the first traces of inflammation.

"From the portal space the sclerosis radiates in different

directions, arising by large bands of connective tissue or irregular tracts which tend to coalesce and to join together the supra-hepatic veins. It thus divides the liver into a great number of irregular rings, comprehending not an entire lobule, but portions of lobules, sometimes fragments of two neighboring lobules. We notice, besides, a certain irregularity in this distribution, and by the side of one small island, in which the cells are but little dis-associated by the newly formed tissue, we see others in which the elements are completely disaggregated. The edges of the sclerosed bands are not cleanly cut, as in the systematic annular cirrhosis. We see sclerosed tracts starting from them which penetrate between the neighboring cells and separate them. These tracts are blended with the walls of the intra-lobular capillaries which they thicken, penetrating sometimes very deeply into the interior of the lobule. If the cirrhosis is of long standing, the rows of cells may be almost completely disaggregated, so as to give to the liver the appearance of a monocellular cirrhosis. The sclerotic process presents in some cases a tendency to diffusion, which appears to be one of its principal characteristics."

It seems to me that a comparison of these two anatomo-pathological forms shows a pathological connection. Does not the idea naturally present itself to the mind that, the hypertrophic cirrhosis of the tuberculous may also invoke for its cause an auto-intoxication of gastro-intestinal origin? While recognizing the fact that tuberculosis, let it be actually represented in the liver by the bacillus of Koch or its toxin, may have a sclerogenic action (the nodular hepatitis would be sufficient to prove this); while admitting that the abuse of alcohol, even at a remote period in the history of the patient, may facilitate this sclerosing action or itself take part in the process, we must also consider the fact that the stomach and intestine are rarely unaffected by the lesion.

The swallowed expectoration contains, so far as microbes are concerned, only the bacillus of Koch, and, so far as regards chemical or bacterian products, only tuberculin. There is frequently some mucous gastritis, dilatation of the stomach, alimentary stasis, and consequent abnormal fermentations. With an organism debilitated like that of a patient with advanced phthisis, the toxic irritations have a more powerful effect, and perhaps a part of the diffused sclerosis is due to poisons of gastro-intestinal origin absorbed by the portal vein. Such a liver is not encountered solely with the tuberculous, M. Sabourin informs me, but also

with a great number of cachectic individuals, cancerous, etc., and these also have an alimentary canal all ready for the abnormal fermentations. I will not dwell upon this aspect of the subject; in order to speak with assurance, it would be necessary to have a series of observations of tuberculous patients in which the condition of the digestive passages had been carefully studied, and by means of which we might be able to establish an evident relationship between the alterations of the alimentary canal and sclerosis of the liver.

What I have just said appears only as a corollary of my thesis, and I should be pleased if some one else would undertake to clear up this uncertain point of the history of hepatic tuberculosis. I will besides repeat what I said at the beginning: I have here considered only one of the anatomo-pathological and clinical forms of dyspeptic cirrhosis. Perhaps there are others, as the case of Kutreff, reported above (Case XXVI), would lead us to believe.

Let this then be taken as a temporary foundation-stone upon which may be built either variants of this type or new forms.

PART III.

Experimentation.

PREVIOUS EXPERIMENTS.

The hope, so frequently disappointed, of realizing with animals the diseases observed with men, has, for forty years past, urged physicians on in the path of experimental pathology. But, on account of the complexity of the morbid act, these attempts have only terminated in approximations or resemblances, and only in a very few cases.

The defective material conditions which every experimenter encounters, the unfitness of the subjects which he unavoidably has at his disposition, the choice and the separation which he is obliged to make in pathogenic causes, sufficiently explain the insufficiency of the results obtained. This is not a reason for renouncing attempts of this kind which at least may be able, if they do not exactly realize our desiderata, to throw some light upon the questions investigated and enable us to comprehend the obscure genesis of our diseases.

To comprehend, is in short all that we desire ; *to see indistinctly*, is now very much. The affections of the liver, and in particular the cirrhotic process, have already tempted the curiosity of many. And, since alcohol appeared to be the principal cause of it, it is with alcohol especially that experiments have been made. I will not enter into the details of the labors of Dahlstrom, Ruge, Duchek, Lallemand, Perrin and Duroy, Kremiensky, Magnan, Pupier, Dujardin-Beaumetz and Audige, Strassman, Grandmaison, who have only obtained cellular lesions in the liver of their animals, in particular steatosis.

The results of MM. Straus and Blocq have been more satisfactory; they have obtained in the portal spaces, around the blood and biliary vessels, a well-marked infiltration of embryonic cells, especially about the terminal branches ; but these lesions

have not gone beyond the initial stage, embryonic, of cirrhosis, which these authors qualify as annular, perilobular, and monolobular. More recently Richter has gone over these experiments and has obtained with the rabbit a peri-supra-hepatic cirrhosis. We will find in the thesis of Laffitte a criticism of all these investigations. The latter author has conscientiously experimented upon thirty-four rabbits to whom he has, for a period of time varying from four days to fifteen months, given wine, alcohol, and absinthe; now these animals have presented some lesions of the liver which have no resemblance to the so-called alcoholic atrophic cirrhosis.

The toxic influence of the alcohol has solely affected the hepatic cells, which eventually almost completely disappear and are no longer represented except by slender protoplasmic filaments with little color and arranged in a plexus. The nucleus has disappeared, the enormously dilated capillaries correspond to the floor of this plexus. This final alteration evolves by little islands which appear on the sections in the form of colorless spots.

The production of these necrotic islands is due to interstitial hemorrhages. The connective tissue is ordinarily intact; in some exceptional cases we see a few more embryonic nuclei than in the normal condition; but this slight irritation appears to be in relation with the deep lesions of the gastric mucous membrane. In fact Laffitte has noticed, as Straus and Blocq had previously done, a constant lesion; hypertrophy of the gastric wall and a thickened mucous membrane, congested, with or without small superficial ulcerations, with or without punctiform hemorrhages. Laffitte is convinced that, in the pathogeny of cirrhosis of the liver, we must attribute an important part to the alterations of the alimentary canal. "The condition of the intestine and stomach," says he, "should be carefully noted in all the cases of sclerotic hypertrophy of the hepatic gland. The acute or chronic irritations of the digestive mucous membrane, by opening a path for the micro-organisms in contact with it or to the poisons produced by these bacteria, may react upon the liver and thus provoke a lasting inflammation of the perilobular spaces."

Independent of alcohol, experiments have been made with but few substances administered by the mouth: direct injection into the portal vein has been more frequently practised. M. Bouchard has shown that *naphtol* in solution in diluted alcohol injected into

the portal vein produces a manifest sclerosis accompanied by a fatty degeneration of the elements (organites).

By injecting urate of soda and lactic acid into the vessels, M. Charrin has succeeded in giving rise to modifications especially affecting the nobler elements. "I have obtained results analogous to those of Pavone," says he, "although with difficulty, by employing bacterian toxins."

I do not mention the angiocholitis and peri-angiocholitis produced by the introduction of microbian cultures into the biliary passages (Haot, Gilbert, and Dominici, etc.). They are connected with the study of infections of the liver.

As to tuberculin, it does not appear, according to the results observed with the patients treated with the remedy of Koch for weeks and months, in increasing doses, that it has any sclerogenic effect upon the liver. The guinea-pigs which Koch inoculated with tuberculin did not present any tendency to hepatic cirrhosis.

PERSONAL EXPERIMENTS.

For purposes of experimentation, among the poisons of the alimentary canal, I have especially chosen those substances which authorities generally believe to be most injurious, and those which, by their physical properties themselves, would appear susceptible of exercising an irritant or toxic action upon the liver.

Thus I have caused rabbits to swallow butyric, lactic, valerianic, acetic, oleic, palmitic, stearic, margaric, and oxalic acids, aldehyde, acetone, pepper (reputed capable of producing cirrhosis), living cultures of *Bacterium coli communis* of various ages and from different sowings, toxins of this microbe prepared from recent cultures or from those of more or less age; lastly, some extract of fæces. As a subject of experimentation I have selected the rabbit, which is easily handled, of which quite a large number can be accommodated in a laboratory, and of which the liver readily becomes sclerosed from causes already known (psorospermosis, biliary infections, etc.); besides, it is this animal in particular which has already served for the experiments with alcohol.

The rabbits, each occupying a separate cage and well cared for, were housed in quite a spacious room contiguous to the laboratory, well ventilated, well illuminated and heated in winter. Their ordinary food has consisted of cabbage, carrots, potatoes, salad, etc. Each animal received every morning, in a Petri box or in a little

crystallizing dish, a ration of bran soaked with the substance the subject of experiment. The solid substances (fatty acids) were dissolved in ether, poured upon the bran, and the ether evaporated; the pepper, ground fresh every morning, was also mixed with the bran.

The animal only received some other food after it had swallowed this first breakfast. The rabbits made no objections to taking the majority of these substances. Valerianic acid, of which the odor is so penetrating and so disagreeable, was nevertheless swallowed after a few days. The greatest difficulty was experienced in making the rabbits take the acetic acid. Two however resigned themselves to eating their bran sprinkled with this substance.

In no case was a gastric tube employed, for, as Laffitte says, we may easily make a false passage and pour the liquid into the trachea; a very serious affair, as we may thus determine gastric lesions, so to speak, traumatic, which it is exceedingly important to avoid. The rabbits were weighed when the experiments commenced and weekly afterwards.

About sixty rabbits were experimented upon, but a certain number died of tuberculosis or refused to swallow the bran sprinkled with the substance under experiment. Forty-three have given the results here recorded. The animals were divided into two series: the first took the substance employed in the experiment without any addition; the second, the same substance with 10 or 20 c.c. of 95 per cent. alcohol. Some of these experiments have lasted more than a year.

CHEMICAL SUBSTANCES.

Experiment 1.

Butyric Acid alone.—*Duration: two months, twenty-eight days.*—Rabbit weighing 1960 grams, healthy, takes every day, commencing May 4, 1893, half a gram of butyric acid with which the bran was sprinkled. May 9th, he no longer has any appetite and only weighs 1785 grams. May 19th he eats a little better and weighs 1710 grams.

May 24th, he eats perfectly well, but he continues to grow thin: weight, 1580 grams. He is timid and keeps in the back part of his cage. June 1st, the urine drawn with a catheter is alkaline, thick; with the microscope we only see some white

Fig. 1.

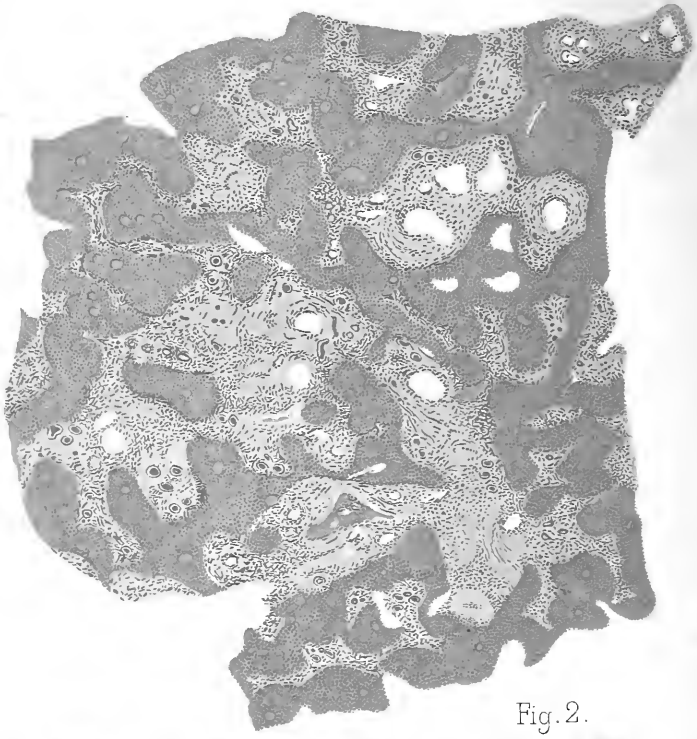
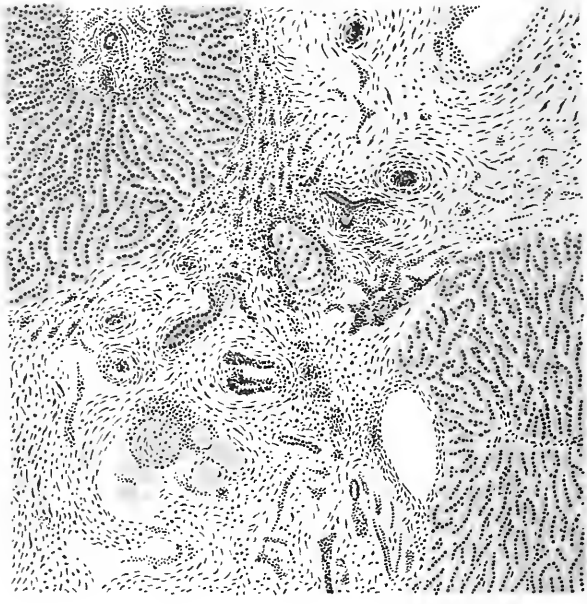


Fig. 2.



Silbermann. Imp. Lemercier Paris. Nicolet lith.

PLATE II.

FIG. 1 (Leitz, oc. 3, objec. 1).—Liver of the Rabbit 10 hours after ligature of the bile-duct.

The liver is completely disarranged (Monkeyed) by the proliferated connective tissue. On the surface, the sclerosed tissue is more abundant than the hepatic parenchyma is solely peripheral; the central vein of the lobule is usually free from sclerosis are united and tend to completely isolate the lobules. This is plainly manifested in the lower portion of the figure.

FIG. 2 (Leitz, oc. 1, objec. 4).

Detail of Figure 1 greatly enlarged, showing a sclerosed portal space, with connective tissue, cul-de-sac cells, and slight proliferation of the biliary canal. The center a little island of hepatic cells encompassed by the sclerosis.

PLATE II.

FIG. 1 (Leitz, oc. 3, objec. 1).—LIVER OF THE RABBIT OF FIRST EXPERIMENT.

The liver is completely disarranged (*bouleversé*) by the proliferated connective tissue. On the surface, the sclerosed tissue is more abundant than in the deeper parts. The sclerosis is solely porto-biliary; the central vein of the lobule is unaffected. The lines of sclerosis are united and tend to completely isolate the lobules; this isolation is especially manifested in the lower portion of the figure.

FIG. 2 (Leitz, oc. 1, objec. 4).

A point of Figure 1 greatly enlarged, showing a sclerosed portal space with abundant connective tissue, embryonic cells, and slight proliferation of the biliary canaliculi. In the centre, a little island of hepatic cells encompassed by the sclerosis.

globules; it contains a little albumin, no urobilin. On June 14th, he only weighs 1365 grams. The urine is normal.

However he gains in weight the next few days and weighs 1640 grams on June 21st. He eats well and appears to be regaining his health. On June 26th, the daily dose of butyric acid was raised to 2 grams. Starting from this date, the rabbit constantly diminished in weight and died Aug. 2d, weighing only 1195 grams.

Autopsy.

Liver weighs 47 grams. It is light brown and marbled with whitish spots of various dimensions, communicating with each other more or less and somewhat below the surface of the organ, like depressed cicatrices. It is very hard on section and the interior of the liver presents the same appearance as the surface. *Stomach* covered with a thick layer of mucus; this removed, we notice that the mucous membrane is swollen and strewn with little ecchymoses; there is no ulceration. Nothing particular in the other organs. The *urine* collected in the bladder is *very acid*, and contains quite a large percentage of albumin but no urobilin.

Microscopic Examination of the Liver (Pl. II, Figs. 1 and 2). —With a slight enlargement (obj. 1, ocul. 1 of Leitz), we can make out that the liver is literally turned topsy-turvy (bouleversé). The connective tissue takes up at least as much space if not more than the tissue proper of the organ. There is no order in its distribution.

The patches of sclerosis, rounded, sinuous, of every shape, furrow the parenchyma in every direction, to the extent of most frequently rendering the lobules unrecognizable. Some cellular groups, lobules or portions of lobules, are encompassed and enclosed in the connective-tissue gangue.

In various places this is perforated by the gaping mouths of the vessels. This is perfectly apparent to the naked eye. On the sections stained with picro-carmine in particular, the bright-red color of the connective tissue contrasts very plainly with the reddish-yellow color of the parenchyma.

With a greater enlargement (obj. 4, ocul. 1 of Leitz), we make out that the proliferation of connective tissue has the portal spaces for its point of departure. At these points we see the blood-vessels, whose walls are completely blended with the surrounding tissue, encompassed with concentric zones of adult connective-tissue fibres.

In this respect it is the same with the biliary canals; from one

vessel to another the zones of sclerosis are merged with each other, and we have large spaces solely formed of close and homogeneous fibrous tissue. Here and there, and principally in the corners formed by the approximation of two lobules, in the vicinity of the hepatic cells, we see a moderate number of newly formed biliary canaliculi. Likewise at these points there is a very marked infiltration of embryonic cells and free diapedesis of leucocytes. The epithelium which lines the biliary canals of a certain calibre is most frequently respected; the lumen of these canals is nowise obstructed and the epithelium has not proliferated; it has also lost nothing of its distinctness. The supra-hepatic veins are generally unaffected; some, however, have one wall slightly thickened.

The cells quite clearly limit the sclerotic patches, but are, however, invaded at the point of contact by an embryonic infiltration. The cellular spaces present their ordinary arrangement. With a very great enlargement (objec. 7, ocul. 1 of Leitz), we can see that there are very different degrees of alteration of the cells. None of them is absolutely normal. The least diseased have yet quite a clear contour, but the protoplasm is slightly granular.

Some have two nuclei. At a more advanced degree, the granular degeneration is accentuated, the contours of the cells blend with each other, and the protoplasm of all the cells forms a continuous granular background. At a yet more advanced stage, there is some vitreous degeneration and frequently a disappearance of the protoplasm; so that at certain points we have some lobules or portions of lobules which present numerous lacunæ throughout their whole extent; the whole resembles a reticulum with quite large meshes, formed by the granular or vitreous protoplasm of the cells which have not yet disappeared. There was no fat. This examination leads to the conclusion that we have here *a type, so to speak perfect, of the atrophic cirrhosis of Laennec.*

Experiment II.

Butyric Acid alone.—*Duration: two months, fourteen days.*—Rabbit, of 1855 grams, healthy, takes every day, beginning May 4, 1893, half a gram of butyric acid. On May 9th, the appetite is moderate and the weight has fallen to 1695 grams. May 16th, he eats a little better and weighs 1590 grams. Until the end he constantly loses weight, save a slight increase of 75 grams from the 14th to the 21st of June.

On June 1st, the urine, drawn with a catheter, contained neither albumin nor sugar, but with the spectroscope plainly gave the *spectrum of urobilin*. June 14th, it was normal. On June 26th, the daily dose of butyric acid was raised to 2 grams. He died July 18th, weighing only 1165 grams.

Autopsy.

The *liver* weighs 34 grams. Absolutely comparable to the liver of Experiment I. The *stomach* is covered with mucus, but presents no ecchymoses. The *kidneys* are small, but do not appear altered. Nothing particular in the other organs. The *urine* collected in the bladder is very acid and contains albumin in large quantity. It is light-colored and limpid.

Microscopical Examination of the Liver.—As in Experiment I, there is a true cirrhosis: the total surface of connective tissue is perhaps a little less. All the other details are absolutely comparable.

EXPERIMENT III.

BUTYRIC ACID AND ALCOHOL.—*Duration: sixteen days.*—Rabbit of 1785 grams, a little thin, takes every day, beginning May 4, 1893, 50 centigrams of butyric acid and 10 c.c. of 95 per cent. alcohol. While diminishing in weight (1610 grams May 9th), he eats well until May 16th; he, however, only weighs 1290 grams; he is depressed; his ears have a tendency to droop. He died May 20th, weighing 1050 grams.

Autopsy.

Liver weighs 34 grams. Same color, same appearance, same consistence as in Experiments I and II. *Stomach* filled with bran. No odor of butyric acid or alcohol. Thick and continuous layer of mucus upon the surface of the mucous membrane of the stomach, which presents slight ecchymotic arborizations. Nothing particular in the other organs. No urine.

Microscopic Examination of the Liver.—Results comparable to those of Experiments I and II, but very much less connective tissue; embryonic infiltration is more pronounced.

EXPERIMENT IV.

BUTYRIC ACID AND ALCOHOL.—*Duration: twenty-one days.*—Rabbit of 1685 grams, not very lively, takes every day, beginning

May 21, 1893, half a gram of butyric acid and 10 c.c. of 95 per cent. alcohol. The urine, drawn with the catheter June 1st, was of normal composition. He died June 10th, weighing only 1070 grams.

Autopsy.

Liver weighs 32 grams. It is violet-red and very much congested: there is a goodly number of whitish spots marbling the parenchyma. The *stomach* is small, contracted; there is neither vascularization nor ulceration. The *kidneys* are small and congested. They unfortunately have not been preserved. The *bladder* is very much distended. The urine which it contains is very acid and of a blood-red color. Under the microscope, numerous red and some white globules. Albumin in abundance. Nothing particular in the other organs.

Microscopical Examination of the Liver.—Same degree of sclerosis of the liver as in Experiment III.

EXPERIMENT V.

BUTYRIC ACID AND ALCOHOL.—*Duration: eight months, fifteen days.*—Rabbit of 1920 grams, healthy, swallows every day, beginning August 5, 1893, 2 c.c. of butyric acid and 20 c.c. of 95 per cent. alcohol. The weight diminished in the first place to 1570 grams; from the 12th of August it gradually increased, and May 22, 1894, the animal weighed 2600 grams. At this date it was killed by the introduction of air into its veins.

Autopsy.

Liver weighs 112 grams. Normal consistence and coloration. *Alimentary canal* presents no appreciable alteration to the naked eye; the mucous membrane of the stomach is a trifle more vascular than normal. Other organs healthy. No urine.

Microscopical Examination of the Liver.—Upon a section stained with picro-carmine, we notice that the cells are markedly increased in size and in a state of fatty degeneration. Their arrangement is abnormal. The protoplasm is scarcely colored, and there are some nuclei in almost the same condition.

In the portal spaces we discern a fibrous radiation hardly distinguishable from the cells. *We ask ourselves if there is not a transformation of the cells into fibrous tissue.* Upon another

section, stained with carmine and hematoxylin, we see some spaces which have a tendency to merge with each other and to circumscribe the lobules with lines of embryonic cells.

Experiment vi.

Butyric Acid and Alcohol.—*Duration: eleven months, eight days.*—Rabbit of 2045 grams, very vigorous, takes every day, beginning June 14, 1893, half a gram of butyric acid and 10 c.c. of 95 per cent. alcohol. At first he increases in weight. June 24th, he weighed 2100 grams. The urine is normal. June 26th, we raise to 2 grams the dose of butyric acid and to 20 c.c. that of alcohol. The animal gradually grew thin until on July 5th it only weighed 1560 grams.

Then, with some oscillations, he gained and weighed 2040 grams on September 16th. During two and a half months he oscillated between 1850 and 2150 grams. Starting from this time he constantly increased in weight up to 2750 grams on May 22, 1894, when he was sacrificed by the injection of air into his veins.

Autopsy.

Liver weighs 82 grams, the animal being killed at the acme of digestion. The organ is of normal consistence and color. All the other organs are healthy, including the stomach.

Microscopical Examination of the Liver.—Simple embryonic infiltration, quite marked, however, of the portal spaces, but the tissue has no tendency to run between the lobules. The *cells* are markedly affected and almost all are in a *very pronounced state of granular fatty degeneration.*

Experiment vii.

Lactic Acid.—*Duration: three months.*—Rabbit of 1850 grams, healthy, takes every day, commencing April 28, 1893, 2 grams of lactic acid. Although eating heartily, he constantly grew thin until May 24th, when he weighed 1350 grams. Urine normal. He afterwards gained in flesh, and, June 21st, weighed 2020 grams. On June 26th, we increased to 6 grams the dose of lactic acid; two days after, the animal had already lost 100 grams. On July 1st, we diminished the dose one half because the rabbit had refused his food the day before. He eats the bran with 3 grams of lactic acid. He became more and more emaciated and died July 29th, weighing only 1230 grams.

Autopsy.

Liver weighs 19.50 gr. Mahogany-brown color; marbled appearance like the liver of Experiments I, II, III, and IV, with butyric acid. Same appearance upon section. The *stomach* appears absolutely normal. The *kidneys* are very small and pale. *Urine* light-colored; neither sugar nor albumin.

Microscopic Examination of the Liver.—The sclerosed tissue, while sufficiently extensive to form large patches at certain points, is, however, less pronounced than in the butyric livers; but there is not a portal space which is not richly infiltrated with embryonic cells invading more or less the adjacent lobules. The cells are little altered.

EXPERIMENT VIII.

LACTIC ACID AND ALCOHOL.—*Duration: one year, twenty-four days.*—Rabbit of 1735 grams, healthy, takes, commencing April 28, 1893, 2 grams of lactic acid and 10 c.c. 95 per cent. alcohol daily. Although eating well, in the first place he lost flesh until May 16th, when he weighed 1470 grams. He afterwards gained until June 21st, when he weighed 1880 grams. The urine was normal. On June 26th, we began to give him 6 grams of lactic acid and 20 c.c. alcohol daily. By July 5th, his weight had been reduced to 1830 grams. Starting from this time, he commenced to gain. From July 11th (2020 grams) to October 31st (2140 grams), oscillations around 2000 with minimum of 1890 grams August 12th. From the 31st of October, 1893, to the 22d of May, 1894, gradual increase to 2950 grams. On this day he was killed by the injection of air into a vein of the ear.

Autopsy.

Liver weighs 90 grams. Consistence and color normal. All the other organs normal, including the stomach.

Microscopic Examination of the Liver.—All the portal spaces are more or less infiltrated with embryonic cells; in some the sclerosis stands out in bold relief, but the cells are principally altered. *Fatty degeneration is general;* in many of the cells the nucleus itself has disappeared; we find fat vesicles in great number. Some cells are enormous, with a very large nucleus; the protoplasm and nuclei are scarcely stained by the carmine and hematoxylin. There is some effusion of blood between the cellular spaces.

EXPERIMENT IX.

VALERIANIC ACID ALONE.—*Duration : seven months, twenty-six days.*—Rabbit of 1640 grams, healthy, takes daily, commencing May 15, 1893, half a gram of valerianic acid. In the first place there was some trouble in making him take the mixture, but afterwards he ate well. At first he grew thin and only weighed 1385 grams on the 14th of June. He afterwards gained and weighed on June 21st, 1555 grams.

On the 26th of June we commenced giving him 2 grams of the acid ; on this day he weighed 1590 grams ; but starting from this day, he diminished in weight, and after some oscillations between 1200 and 1300 grams, he died, January 11, 1894, during the night, only weighing 1135 grams.

Autopsy.

Liver weighs 35 grams ; it is very much congested, firm ; we see no contractile tissue at the surface or upon section. The *lungs* are congested. The *stomach* is red, but there are no ecchymoses or ulcerations. The *kidneys* are large and pale. The *urine* neutral, containing neither sugar nor albumin.

Microscopical Examination of the Liver.—Infiltration evident, but moderate, of the portal spaces ; in some, fibrous tissue. All the cells in a state of granular fatty degeneration ; the nuclei are fairly well stained ; lacunæ here and there, some cells having completely disappeared.

EXPERIMENT X.

VALERIANIC ACID ALONE.—*Duration : one month, eighteen days.*—Healthy rabbit of 1850 grams takes every day, commencing May 30, 1893, half a gram of valerianic acid. June 6th, he weighs 1890 grams, but starting from this date he grew thinner and fell to 1585 grams on June 21st. On the 26th of June, we increased the amount of acid to 2 grams. The animal continued to grow thin, and died on July 26th, weighing only 995 grams.

Autopsy.

Liver weighs 40 grams. Mahogany-brown color, with the appearance of Experiment VIII. The *stomach* is congested, but without ecchymoses or ulcerations. The *kidneys* are large and pale. The *urine* is very acid, and contains albumin in appreciable quantity.

Microscopic Examination of the Liver.—Very pronounced sclerosis of a goodly number of portal spaces; others are less sclerosed; the remaining spaces are infiltrated with embryotic cells. The hepatic cells are in quite an advanced state of fatty degeneration, but less diseased however than in the liver of Experiment VIII.

Experiment XI.

Valerianic Acid alone.—*Duration: one month, nine days.*—Very vigorous rabbit, weighing 2530 grams, commencing April 19, 1893, takes daily half a gram of valerianic acid. He made some objections at first, but afterwards became accustomed to the diet. He rapidly grew thin, although eating very well; he is less lively than at the beginning of the experiment. On the 28th of July, he died, weighing only 1560 grams.

Autopsy.

Liver weighs 41 grams. Absolutely comparable to the preceding one. The *stomach* is very much thickened and corrugated, shrunken towards the œsophagus; the mucous membrane is red, in the œsophageal region especially, but presents neither ecchymoses nor ulcerations. *Lungs* congested. *Kidneys* large and pale. No urine.

Microscopic Examination of the Liver.—Embryonic infiltration of all the portal spaces with tendency to surround the lobules (annular cirrhosis). Cells in a condition of granular fatty degeneration, sometimes very advanced; the majority of the nuclei are, however, quite well stained.

Experiment XII.

Valerianic Acid alone.—*Duration: eighteen days.*—Rabbit of 1620 grams, puny, takes every day, commencing April 19, 1893, half a gram of valerianic acid. The first few days he objected to swallowing the bran sprinkled with the acid, undoubtedly on account of the odor. However, at the end of a few days there was no difficulty. He rapidly grew thin and died May 7th, weighing 950 grams.

Autopsy.

Liver small, weighs 37.50 grams; reddish-brown; hard upon section; shows some patches comparable to those of the butyric

acid livers, but of very much darker color, much less clearly outlined upon the rest of the parenchyma, and less confluent. The *spleen* is very small. The *lungs* are very much congested. The *stomach* has a strong smell of valerianic acid; its walls are little thickened; there are neither ecchymoses nor ulcerations. *Kidneys*, large and pale. No *urine*.

Microscopic Examination of the Liver.—Some portal spaces are plainly sclerosed; others are infiltrated with young cells. The hepatic cells are commencing to undergo fatty degeneration with contraction.

EXPERIMENT XIII.

VALERIANIC ACID AND ALCOHOL.—*Duration: one year, nineteen days.*—Rabbit of 2070 grams, robust, takes daily, commencing May 3, 1893, half a gram of valerianic acid and 10 c.c. of 95 per cent alcohol. He made no objections to the mixture. He immediately began to grow thin and only weighed 1670 grams on the 16th of May.

He afterwards gained, and weighed, on June 21st, 2050 grams. On June 26th, we increased the amount of valerianic acid to 2 grams and that of alcohol to 20 c.c. Fresh fall in weight until July 5th, when the animal weighed 1770 grams. Then he gained, and after some fluctuations in weight, positively grew fat. He was killed May 22, 1894, by the injection of air into the veins; weight, 3100 grams.

Autopsy.

Liver weighs 100 grams. Color and consistence normal. All the other organs sound.

Microscopic Examination of the Liver.—Very slight embryonic infiltration of the portal spaces. Very advanced granular fatty degeneration of the hepatic cells; many have entirely disappeared.

EXPERIMENT XIV.

ACETIC ACID ALONE.—*Duration: one month, six days.*—Rabbit of 1580 grams, healthy. We mix with the bran 5 c.c. of laboratory acetic acid. It is only with difficulty that we succeed in making the rabbit take this mixture; he only concludes to eat it when forced by hunger. At the time that he eats it, the bran has yet a strong odor of acetic acid. He only finally accustoms him-

self to this alimentation about June 15th. On the 14th, he weighed 1550 grams; the 21st, 1670 grams. Starting from this time, he quickly lost flesh and died July 5th, weighing only 1040 grams.

Autopsy.

Liver weighs 35 grams. Mahogany-brown, with some contracted portions. Very hard on section. *Stomach* red, but without ecchymoses or ulcerations. Nothing particular in the other organs. *Urine* very acid, containing albumin.

Microscopical Examination of the Liver.—Large bands and patches of sclerosis as in the butyric livers. The cells are markedly affected by granular degeneration. In certain very extensive regions, the nuclei themselves no longer form anything but a sort of dust colored by the hematoxylin, upon an amorphous background stained rose color by the eosin.

EXPERIMENT XV.

ACETIC ACID AND ALCOHOL.—*Duration: twenty-three days.*—Rabbit of 1960 grams, healthy, takes every day, commencing June 3, 1893, 5 c.c. of acetic acid and 10 c.c. of 95 per cent alcohol. He accepts this food at the beginning of the third day. He grew thin and died the 26th of June, weighing 1480 grams. He had a large belly.

Autopsy.

Liver weighs 42 grams. Reddish-brown coloration with some light spots moderately confluent. Firm consistence. *Stomach* distended and red, without ulceration or ecchymoses. *Intestine* distended. No liquid in the peritoneum. *Kidneys* pale. *Urine* limpid, very acid with some albumin.

Microscopical Examination of the Liver.—Alterations much less pronounced than in the preceding case. All the portal spaces are either moderately sclerosed or infiltrated to a great extent with embryonic cells. The cells are in a condition of commencing granular degeneration; their nuclei, however, are quite well stained.

EXPERIMENT XVI.

FATTY ACIDS.—*Duration: eight months, twenty-six days.*—Vigorous rabbit of 1780 grams, commencing May 4, 1893, takes

every day half a gram of oleic acid and as much palmitic acid. The acids are dissolved in ether and the solution poured upon the bran and allowed to evaporate. After losing weight until May 16th (1580 grams), the animal gained in flesh and on June 21st, weighed 1950 grams.

Commencing June 26th, 2 grams of each of the following substances were daily ingested:

Oleic acid
Palmitic acid
Margaric acid
Stearic acid.

There was again a loss of weight and on July 5th the animal weighed 1655 grams. From this time on there was an increase until September 16th, when his weight was 1910 grams. He only attained the weight of 1950 grams after having become accustomed to the first doses of acid. He has always had a good appetite and his ration of fresh vegetables has frequently exceeded that of the other animals. From October 10th to December 17th, his weight oscillated between 1800 and 1860 grams. About the end of December, the animal commenced to grow thin; January 9, 1894, he weighed only 1400 grams and died, January 27th, weighing 1365 grams.

Autopsy.

Moderate tuberculosis of the *lung*. *Liver* weighs 46 grams. Grayish color; a little hard upon section. The *alimentary canal* presents no peculiarity; there is no peritoneal tuberculosis.

Microscopical Examination of the Liver.—Some solitary tubercles in the hepatic tissue; some others along the vessels. No other proliferation except a very moderate infiltration at some few points where two or three tubercles are united, in the vicinity of the portal spaces. The cells are very plainly in a condition of granular fatty degeneration.

EXPERIMENT XVII.

Fatty Acids and Alcohol.—Duration: one year, sixteen days.—Rabbit of 1480 grams daily takes, commencing May 4, 1893, half a gram of oleic and as much palmitic acid dissolved in ether and sprinkled on the bran, and also 10 c.c. 95 per cent. alcohol. Weight stationary until May 9th, when he weighed 1496 grams.

In the first place he diminished a little in weight. May 24th, he weighs 1340 grams; then he increased in weight to 1670 grams. Commencing June 26th, he took until death:

Oleic acid.....
Palmitic acid.....
Margaric acid.....
Stearic acid..... } (aa) 2 grams.
95 per cent. alcohol....20 c.c.

Fresh loss of weight; the animal weighing 1590 grams, July 5th. For a month and a half after, he oscillated in weight, and weighed, July 11th, 1760 grams; July 21st, 1805 grams; August 5th, 1740 grams; August 12th, 1800 grams; August 26th, 2000 grams. From this date he gradually gained in weight, notwithstanding the daily ingestion of his 8 grams of fatty acids, and his 20 c.c. of alcohol.

On the 28th of May, 1894, he weighed 2600 grams. He was killed on this date by the injection of air into the veins. There was never any sugar or albumin in the urine, but at several times it gave the characteristic spectrum of urobilin.

Autopsy.

Liver weighs 82 grams. It is remarkably tri-lobed, as if foliated. Its color was normal. All the other organs, including the stomach, present no alterations.

Microscopic Examination of the Liver.—No trace of connective-tissue proliferation. The cells are in quite an advanced state of granular fatty degeneration. Here and there, the trabecular arrangement is preserved, but in one space we can no longer distinguish the cells from each other except by their nuclei. These cells are either hypertrophied to the extent of touching those of the neighboring space, or, on the contrary, diminished in volume, so that the spaces are very narrow, with very large openings between them; they resemble a net with large meshes. Lastly, at certain points, in patches, the protoplasm of all the cells is run together, and the nuclei, pale and swollen, stand out on a uniform and almost amorphous background.

EXPERIMENT XVIII.

ACETONE.—*Duration: seven days.*—Rabbit of 1620 grams takes, commencing July 19, 1893, a daily dose of 10 c.c. of acetone.

He died on July 25th. His *urine* contained a large amount of albumin.

Autopsy.

Liver weighs 30 grams; it is very much congested. The *kidneys* are very large and pale. The mucous membrane of the *stomach* is very red, but there are no ecchymoses or ulcerations.

Microscopical Examination of the Liver.—The cells, without, being granular, are cloudy; there is a lack of clearness of outline, *stumped*, so to speak. Around some biliary canals, there is a thin ring of sclerosis, undoubtedly due to a slight degree of ascending angiocholitis, anterior to the experiment. Independently of this, no proliferation of connective tissue.

Microscopical Examination of the Kidneys.—The cortical portion is very much diseased. All the convoluted tubules have their epithelia swollen to the extent of closing up the lumen; the protoplasm is granular or simply cloudy; the nucleus is extremely pale even in the hematoxylin preparations. Of the glomeruli, some have kept their normal size, but in the cavity of the glomerulus we find a granular detritus which appears to be albuminous; others are very much swollen, and the cavity is obliterated by the contact of the epithelia.

The straight tubes are less affected; the epithelium is scarcely swollen; almost everywhere they contain the same granular detritus mentioned above. In a word, well-marked epithelial nephritis.

Experiment xix.

Acetone.—*Duration: seven days.*—Rabbit of 2130 grams, commencing July 4, 1893, takes daily 10 c.c. of acetone. He died on the morning of July 11th, weighing 1530 grams (he lost 600 grams in seven days). The *urine*, slightly acid, contained a large amount of albumin.

Autopsy.

Liver weighs 53 grams; it is very much congested, violaceous in hue. The *kidneys*, the right one especially, are enormous. The mucous membrane of the *stomach* is swollen, red, and as if pigmented.

Microscopic Examination of the Liver and Kidneys.—Absolutely comparable to that of the preceding experiment.

Experiment xx.

Acetone.—*Duration: sixteen days.*—Rabbit of 1480 grams takes every day from July 19th to August 4, 1893, 4 c.c. of acetone. He died on August 4th. The urine, strongly acid, contains a large amount of albumin, no sugar. Under the microscope we find some red and white globules.

Autopsy.

Liver weighs 21 grams. An incident happened at the beginning of the autopsy which prevented me from examining the other organs, and when I desired, some hours later, to continue the examination, I found that they had been thrown away.

Microscopical Examination of the Liver.—We notice a certain degree of embryonic sclerosis, as much venous as biliary, very marked in some portal spaces.

The cells are unrecognizable, entirely granular, and confounded with each other. It is probable that the kidneys would have presented alterations analogous to those of the kidneys of the two preceding animals.

Experiment xxi.

Aldehyde.—*Duration: six months, twenty-three days.*—Rabbit of 2030 grams. On June 29, 1893, some bran mixed with 10 c.c. of aldehyde was placed before him. He refused this food until the 15th of July, and grew thin during this time, as we gave him very little to eat; July 5th, he weighed 1770 grams. On the 15th of July, he decided to swallow his aldehyde. His weight oscillated for six months, and in a very irregular manner, between 1935 and 1510 grams. He finally died on January 28, 1894, weighing 1345 grams. His urine never contained either sugar or albumin.

Autopsy.

Liver weighs 22 grams; it is dark brown. The *kidneys* offer nothing particular to the naked eye. The *stomach* is small, contracted, thickened; the mucous membrane presents no appreciable alterations.

Microscopical Examination of the Liver.—Moderate embryonic connective-tissue proliferation about some small portal spaces. The cells are in a very manifest condition of granular degenera-

tion; if we can yet here and there distinguish the spaces, the protoplasm is distintegrated and the cells have lost their contour; we find many free granulations.

Experiment xxii.

Oxalic Acid.—*Duration: one month.*—Rabbit of 1905 grams, commencing June 2, 1893, takes daily 25 centigrams of oxalic acid. He diminished in weight, and on June 14th, weighed 1755 grams. He then began to gain, and reached 1805 grams on June 21st. Dating from the 24th, we increased the dose to 1 gram, but the animal only took part of it and refused the remainder. He nevertheless grew thin, and died July 3d, weighing 1105 grams. *Urine*, very acid, contains a little albumin.

Autopsy.

Liver weighs 33 grams; it is brown. The *kidneys* are a little increased in size. There is only some diffused redness of the mucous membrane of the *stomach.*

Histological Examination of the Liver.—Ascending angiocholitis of the large biliary trunks, undoubtedly consecutive to the gastro-intestinal inflammation. Some interlobular veins in the small spaces have a ring of sclerosis already formed or some embryonic infiltration. The cells are completely degenerated, disintegrated, blended with each other.

Histological Examination of the Kidneys.—Cloudy swelling of the epithelium of the convoluted tubules and of the ascending branches of Henle.

Experiment xxiii.

Oxalic Acid.—*Duration: one month.*—Rabbit of 1700 grams takes daily, commencing July 5, 1893, half a gram of oxalic acid. He increased in weight until July 11th, when he reached 1930 grams. From this time he diminished in weight and died Aug. 4th, weighing 1110 grams. *Urine*, very acid, contains some albumin.

Autopsy.

Liver weighs 40 grams, reddish-brown. *Kidneys* large and pale.

Microscopic Examination of Liver and Kidneys.—Absolutely comparable to the preceding case.

EXPERIMENT XXIV.

PEPPER ALONE.—*Duration: twenty-seven days.*—Rabbit of 1910 grams eats every day, mixed with some bran, half a gram of pepper freshly ground, commencing June 6, 1893. He rapidly grew thin, and died July 3d, weighing 1575 grams. There was no urine.

Autopsy.

Liver weighs 61 grams; it is very much congested, violaceous in color. The *kidneys* are also markedly congested and increased in size. The *stomach* is distended, thinned, but presents no alterations of the mucous membrane.

Microscopical Examination of the Liver.—Well marked, fully developed porto-biliary sclerosis, with tendency to penetration of the lobules. Moderate formation of biliary canaliculi. Cells in a state of granular degeneration.

Microscopic Examination of the Kidneys.—Not an epithelial cell but is swollen and granular, and in some tubes the cells are completely disintegrated. Embryonic proliferation of the connective tissue; the coats of the arteries are markedly thickened.

EXPERIMENT XXV.

PEPPER AND ALCOHOL.—*Duration: eleven months, sixteen days.*—Rabbit of 1820 grams eats every day, commencing June 6, 1893, half a gram of freshly ground pepper mixed with some bran, upon which were sprinkled 10 c.c. of alcohol. At first the animal grew thin, and on June 14th, weighed 1630 grams. Then he increased in weight up to 1870 grams on June 21st, but he again lost weight, the amount of alcohol having been increased to 20 c.c. June 26th. He fell to 1240 grams August 5th. From this time he gained and increased in weight up to May 22, 1894, when he was killed by the injection of air into the veins, then weighing 2550 grams.

Autopsy.

Liver weighs 80 grams. Coloration normal. Nothing special in the other organs.

Microscopical Examination of the Liver.—Some portal spaces with well marked embryonic infiltration. The cells are very much affected by the alcohol and have undergone granular fatty degeneration, especially complete in the peripheral portions of the

lobules; in the vicinity solely of the central vein, we find the trabecular arrangement yet preserved, with some cells, the protoplasm of which still takes the stain, but in an irregular manner, in spots. Everywhere else the cells, very pale, are completely distorted, turned topsy-turvy, and only present to the eye a background marbled with yellow and rose color or a faint tint of violet, upon which the nuclei, quite well preserved, stand out in bold relief.

LIVING CULTURES OF BACTERIUM COLI COMMUNIS.

Before experimenting upon rabbits with intestinal microbes, it was proper that we should know, from a bacteriological point of view, what were the contents of their alimentary canals. It was natural to give them cultures of such microbes as we ordinarily encounter with the normal rabbit, so as to approximate as closely as possible to that which takes place with man when there is produced with him an auto-infection of gastro-intestinal origin.

It was a sort of artificial auto-infection which I have endeavored to realize with the rabbit. Now it is the *Bacterium coli* which I have invariably found in the intestinal canal of this animal, most frequently in a condition of purity. It is there presented with its most clearly marked characteristics: peculiarities of culture, indol reaction, coagulation of milk, fermentation of lactose, and very great mobility especially, which, as we know, is a guarantee of its vitality and virulence. It is, then, alone with the *Bacterium coli* that I have experimented, and the *Bacterium coli* coming from the intestine of the rabbit itself. We took a ball of rabbit dung as fresh as possible, cut it in two with a heated instrument, and from its centre charged a platinum wire with material to infect a culture tube of bouillon; resowing in another tube of bouillon and upon solid media at the end of twelve to twenty-four hours. The first culture was generally pure; the second one was always so. In order to realize different conditions of virulence and vitality, I gave cultures of different ages to my rabbits. Some ingested *a continuous living culture*, that is, taken from the same vessel in which the original culture was still progressing; others took *a living twenty-four-hours-old culture from direct sowing*, that is, a culture fresh and renewed daily. Lastly, to the remainder of the rabbits we administered *a living culture twenty-four hours old obtained by successive resowings daily*.

As an exception, one of my animals ingested a culture of *Bacterium coli* obtained from the fæces of a healthy man.

EXPERIMENT XXVI.

CONTINUOUS LIVING CULTURE OF BACTERIUM COLI COMMUNIS.—*Duration: twenty-five days.*—Rabbit of 1870 grams, commencing April 19, 1893, daily swallowed half a cubic centimetre of the pure culture mixed with its bran. It rapidly grew thin and on the morning of May 14th, we found it dead in its cage. It then weighed 1205 grams.

Autopsy.

Liver weighs 30.5 gr. The other organs present no apparent alteration; the mucous membrane of the *stomach* seems normal.

Microscopic Examination of the Liver.—Ascending angiocholitis of the large trunks with very pronounced biliary sclerosis; in the small portal spaces, slight embryonic infiltration as much portal as biliary; no organized connective tissue as with the large trunks. The cells are very variously affected; we notice all degrees of cellular necrosis, from simple cloudiness, with or without swelling, up to disintegration of the protoplasm into a substance which is no longer even granular, a sort of vitrification, without precise limit of cellular contour. Other cells are simply smaller or larger than normal, without appreciable change of the protoplasm. The spaces are again met with in the vicinity of the central vein and also, in many lobules, as far as half of the diameter.

The nuclei are brightly stained: there were no preparations made with Flemming's reagent, so that it was impossible to say if they were in a condition of karyokinesis; we can simply presume it from their bright color. The cellular lesions are not presented in the form of circumscribed islands but are irregularly disseminated: their location however is constant; they affect the peripheral half, if not two thirds of the lobule.

EXPERIMENT XXVII.

CONTINUOUS LIVING CULTURE OF BACTERIUM COLI COMMUNIS.—*Duration: thirty-five days.*—Guinea-pig of 290 grams daily ingested, from April 19, 1893, half a cubic centimetre of pure culture. We found him dead on the morning of May 24th, weighing only 205 grams.

Autopsy.

Liver weighs 11 grams; it is of normal consistence and color. The *stomach* is absolutely normal, also the intestine. No other organ presents any apparent alteration.

Microscopic Examination of the Liver.—The walls of the blood-vessels of a large number of portal spaces are thickened, with slight peri-vascular embryonic infiltration. The alteration of the cells, although less pronounced than in the preceding experiment, is absolutely analogous.

EXPERIMENT XXVIII.

CONTINUOUS LIVER CULTURE OF BACTERIUM COLI COMMUNIS.—*Duration: twenty-one days.*—Rabbit of 1765 grams, commencing May 20, 1893, takes daily 2 c.c. of pure culture. On June 10th, in the evening, convulsive phenomena for three hours. At 6 P.M., the rectal temperature was 36°. 7 C.; at 8 P.M., 34°. 1 C. He died at 8.30 P.M. His weight was 1220 grams.

Autopsy.

Liver weighs 41 grams; of brownish-red color; its consistence seems normal. The *stomach* is a little thickened and contains a large quantity of mucus. The *intestine* presents nothing abnormal. The *kidneys* appear normal to the naked eye. The *bladder*, very much distended, contains a colorless, alkaline urine, slightly cloudy, with a small amount of albumin. The preparations of the liver and kidneys were unfortunately mislaid and they were not examined microscopically.

EXPERIMENT XXIX.

CONTINUOUS LIVING CULTURE OF BACTERIUM COLI COMMUNIS.—*Duration: one month, thirteen days.*—Rabbit of 1630 grams takes daily, commencing June 15, 1893, 2 c.c. of pure continuous culture of *human* B. C. C. He died on the 28th of July, weighing only 1220 grams. At 3 P.M., the rectal temperature was 36°. 3 C.; at 7 P.M., 34°. 5 C. Dead a few moments after.

Autopsy.

Liver weighs 38.50 gr. Brown color. Nothing particular in the other organs.

Microscopic Examination of the Liver.—Ascending angiocholitis of the large trunks and very pronounced biliary sclerosis of the large spaces. In the spaces of medium calibre, we clearly see peri-and endophlebitis with obliterating tendency. Here and there we find central hemorrhages, likewise simple congestion, the red globules filling the inter-trabecular capillaries or rather the spaces still remaining free between the cells, as the intervals are not always recognizable. The cells present alterations analogous to those of Experiment XXVI.

Experiment XXX.

Living Culture 24 Hours Old from Direct Sowing with B. C. C.—*Duration: thirteen days.*—Rabbit of 1855 grams took daily, from May 4, 1893, half a cubic centimetre of pure culture. On May 16th, the animal commenced to throw its head backward, momentarily being in a condition of opisthotonos. He is very thin, weighing only 1200 grams. On May 16th, at 9 P.M., his rectal temperature was 35°. 4 C.; at 4 A.M., 34°. 6 C. He died at 7 A.M. in a condition of opisthotonos.

Autopsy.

Liver weighs 28 grams. Normal color, but the tissue is friable and nowhere hard upon section. The mucous membrane of the *stomach* is here and there red, but not at all ulcerated. Its walls are considerably thickened beneath the mucous membrane; we might call it a neoplastic infiltration. The *intestine* presents nothing particular. The *spleen* is small. The blood of the heart contains some stumpy and mobile *Bacter.* coli.

Microscopic Examination of the Liver.—Ascending angiocholitis of the large trunks, but much less marked than in the preceding experiments. No connective-tissue proliferation in the portal spaces. The cells are principally affected. They are reduced to a sort of granular dust forming a uniform background for the nuclei. Upon some preparations made with Kuhn's blue, with an immersion lens, we very well see the vesicular condition of these nuclei, of which the chromatic substance is sometimes divided and collected at the two poles, sometimes scattered haphazard in the nucleus. At certain points the trabecular arrangement is still preserved, but for the nuclei alone; the cellular protoplasm has almost entirely disappeared and the rows of nuclei form a delicate

network with large meshes ; it would seem as if there were only the skeletons of the cells still remaining. At the first glance, we would imagine that we were examining a section of pulmonary tissue.

Experiment xxxi.

Living Culture 24 Hours Old Directly Infected with B. C. C.—*Duration : one month, twenty-five days.*—Rabbit of 1345 grams, commencing May 20, 1893, daily takes 1 c.c. of pure culture. He gradually grew thin, and on June 21st, weighed 1185 grams.

Shortly afterwards we observed an abscess the size of a walnut on his left flank. This opened externally on June 27th, and gave exit to a thick, odorless pus which contained no micro-organisms, a culture medium infected with this pus remaining sterile. Antiseptic dressing. On the 11th of July, the animal weighed 1075 grams. July 15th, he became cold, but had no convulsions ; possibly he had some the evening before or during the night. At 8 A.M., the rectal temperature was 35°.8 C.; at 2 P.M., 34°.3 C. The animal died at 3 P.M., weighing 985 grams.

Autopsy.

Liver weighs 28.50 grams. Tissue very friable. The pyloric portion of the *stomach* is injected ; nothing abnormal about the *intestine.* The *lungs* are very much congested. The *kidneys* appear normal to the naked eye.

Microscopic Examination of the Liver.—Ascending angiocholitis of the large trunks, but without well-pronounced sclerosis ; in the medium-sized portal spaces a very slight porto-biliary embryonic infiltration. The cells, not so much disintegrated as in the liver of the animal of the preceding experiment, do not the less present the very profound alterations of granular degeneration ; the trabecular arrangement is preserved at a greater number of points. The intra-lobular congestion is very marked ; the red globules of the central capillaries of the lobule form a large circular yellow spot around the central vein.

Microscopic Examination of the Kidneys.—There is cloudy swelling of all the epithelial cells, but the alteration is most marked in the convoluted tubules ; there the lumen is completely obliterated by the swollen cells, or, if this is re-established, it is by the death of the whole central portion of the degenerated cell, the base

alone remaining with the nucleus and presenting an irregular disintegrated border.

We besides observe an intense capillary inflammation with commencing connective-tissue proliferation.

Microscopic Examination of the Lungs.—The alveoli were completely filled with blood; the pulmonary epithelium is in place, but the nuclei are very brightly stained and increased in size; the capillaries are gorged with blood and are intensely inflamed at certain points. No other considerable alteration.

Experiment xxxii.

Living Culture 24 Hours Old—Successive Resowings of B. C. C.—*Duration: eighteen days.*—Rabbit of 1995 grams, beginning May 4, 1893, daily takes half a cubic centimetre of pure culture. Every day we re-infected a fresh tube from the tube of the day before. May 9th, the rabbit weighed 1780 grams and the amount of culture was increased to 2 c.c. May 16th, he weighed 1405 grams. We found him dead on the morning of May 22d.

Autopsy.

Liver weighs 65 grams; it is congested, violet-red, and of firm consistence. The *stomach*, greatly distended, presents a thick layer of mucus adherent to the mucous membrane and forming as it were a second pocket for the food. Very numerous ecchymoses over the whole surface of the mucous membrane. The *intestine* presents nothing abnormal. The *kidneys* appear healthy to the naked eye. The *spleen* is *small*, elongated.

Microscopical Examination of the Liver.—Ascending angiocholitis with very marked sclerosis of the large trunks.

In the portal spaces of medium and small calibre, very plain embryonic connective-tissue infiltration; some supra-hepatic veins also show commencing sclerosis. Very marked degeneration of cells as in the livers of the animals of the preceding experiments.

Microscopic Examinations of the Kidneys.—Same alterations as in the preceding experiment; the capillary inflammation is, however, less intense.

Experiment xxxiii.

Living Culture 24 Hours Old from Successive Reinfections of B. C. C.—*Duration: one month, twenty-four*

days.—Rabbit of 1605 grams, beginning May 23, 1893, daily takes 2 c.c. of pure culture. He gradually grew thin, and, July 11th, weighed 1340 grams. On July 16th, the animal became cold: at 11 A.M., the rectal temperature was 34°. 6 C.; at 1 P.M. 33°.9 C. Death took place at 2 P.M.

Autopsy.

Liver weighs 25 grams; it is violet-red. The *stomach, intestine, and kidneys* present nothing in particular to the naked eye. The *spleen* is large. The urine collected in the *bladder* is pale, without sugar or albumin.

Microscopic Examination of the Liver.—Slight ascending angiocholitis with moderate sclerosis of the large spaces; the small spaces present a very slight porto-biliary embryonic infiltration. The capillaries, very much distended, are engorged with blood. The blood itself is extravasated at various points and forms little circular hemorrhagic centres, especially at the junction of the central veins. The cells are entirely degenerated and compressed laterally by the distended capillaries.

Microscopical Examination of the Kidneys.—Epithelial alteration comparable to that of the kidneys of the animal of the preceding experiment.

COLI-TOXIN.

By coli-toxin, I understand the product obtained by the filtration of bouillon cultures of the *Bacterium coli communis.* When these experiments were made I was not sufficiently well equipped to be able to manufacture a very large quantity of these filtered cultures; also I was compelled to keep the coli-toxin of the 48 hour cultures for the experiments which I had simultaneously undertaken in order to demonstrate the hypo-thermic action of cultures of bacillus coli living and filtered.

To the rabbits under experiment I have administered by way of the mouth the filtrates of cultures eight days and a month old. Everything leads me to believe that the toxins of cultures a little old are less active than those of recent cultures. It was then preferable to have recourse to the former in order to keep the animals a longer time under experiment and consequently to approximate more closely to the condition of a patient through whose liver are daily passing small amounts of coli-bacillary poison elaborated in his intestine. With

the living cultures of bacillus coli I gave no alcohol, fearing that it might affect in some way the vitality of the culture. With coli-toxin, I thought there was no objection to administering both it and alcohol at the same time to some rabbits. The cultures of bacillus coli were filtered through Chamberland filters under mercurial pressure, employing an apparatus manufactured for me by Alvergniat Bros. After each filtration, we assured ourselves, both by direct examination and cultures, that the filtrate contained no bacilli: if necessary a second filtration through the porcelain filter gave a liquid absolutely sterile. The toxins obtained were preserved in Roux's oven, and if, perchance, they happened to grow, we immediately stopped their use.

EXPERIMENT XXXIV.

COLI-TOXIN 8 DAYS OLD.—*Duration: one month, six days.*—Rabbit of 1850 grams, commencing June 4, 1893, takes daily half a cubic centimetre of coli-toxin. June 26th, the animal weighs 1685 grams. Commencing at this time the dose was raised to 2 c.c. The rabbit died July 10th at 10 A.M., weighing only 1240 grams and with a temperature of 35°. 8 C.

Autopsy.

Liver weighs 49 grams. Color pure brown. Manifest congestion. Nothing particular about the *stomach* or *intestine*. *Urine*, slightly acid, contains neither sugar, albumin, nor urobilin.

Microscopic Examination of the Liver.—Slight ascending angiocholitis; in the small and medium portal spaces, slight porto-biliary embryonic connective-tissue proliferation which we also find on a goodly number of supra-hepatic veins. The cellular alterations are absolutely comparable to those of the livers of the rabbits previously examined which took living cultures. The capillaries are dilated and filled with blood globules, especially in the direct vicinity of the central veins or of the large supra-hepatic veins.

EXPERIMENT XXXV.

COLI-TOXIN OF 8 DAYS AND ALCOHOL.—*Duration: one month five days.*—Rabbit of 1930 grams, beginning June 4, 1893, takes daily half a cubic centimetre of toxin and 20 c.c. of alcohol. It was found dead on the morning of July 10th, weighing 1500 grams.

Autopsy.

Liver weighs 51 grams; it is reddish-brown, very much congested. The *stomach* is marbled and streaked with red lines; the *intestine* presents some ecchymoses. The *urine* is straw-color, limpid, slightly acid, and contains a little albumin.

Microscopic Examination of the Liver.—Slight ascending angiocholitis with very pronounced sclerosis of the large trunks. A veritable sanguineous inundation of the liver, to such an extent are the capillaries distended and gorged with blood; there are some places where there is a true rupture, turning the cells topsy-turvy and lacerating the hepatic tissue.

Some vessels of a certain calibre, completely filled with red globules, contain networks of fibrin. As to the cells, they are reduced almost to their nuclei at the points where the capillary distension is extreme, where the trabecular arrangement is still preserved; elsewhere they have completely disappeared, protoplasm and nucleus; we find only a mass of granulations more or less dark, mingled with red globules. In a few cellular groups only there is a little fatty degeneration.

EXPERIMENT XXXVI.

COLI-TOXIN OF 1 MONTH.—*Duration: one month, six days.*—Rabbit of 1360 grams, commencing May 27, 1893, takes daily half a cubic centimetre of coli-toxin. June 26th, the animal weighs 1170 grams. At this date the amount of toxin was increased to 2 c.c. On the morning of July 3d, the animal was found dead, weighing 1000 grams.

Autopsy.

Liver weighs 28.5 grams. Dark brown, congested. The *stomach* is contracted without apparent alteration. The *lungs* are very much congested.

Microscopic Examination of the Liver.—Ascending angiocholitis with very extensive intense sclerosis of the large spaces. In the small and medium spaces, porto-biliary embryonic connective-tissue proliferation. Capillary dilatation and sanguineous stasis less pronounced than in the preceding livers; no hemorrhagic centres. Always the same cellular alterations.

EXPERIMENT XXXVII.

AT FIRST INTRA-VENOUS INJECTION OF 20-DAY COLI-TOXIN, THEN COLI-TOXIN OF 1 MONTH.—*Duration: one month, fourteen*

days.—Rabbit of 1770 grams received in the vein of the ear 4 c.c. of 20-day coli-toxin; he stood the injection but grew thin. On July 5th, he was better, weighing 1675 grams. Beginning at this date he daily took a 1 c.c. of 1-month coli-toxin. The supply of coli-toxin being exhausted July 11th, he went 13 days without taking any. He continued, nevertheless, to grow thin: weight, 1450 grams July 11th; July 21st, 1110 grams. From July 24th to July 27th, when he died in a state of hypothermia, he daily took 1 c.c. of toxin. At 9 A.M., the rectal temperature was 34°.5 C. Died at 2 P.M., weighing 850 grams.

Autopsy.

Liver weighs 22 grams. *Kidneys* very large. *Stomach* presents nothing abnormal. *Lungs* very much congested. No urine.

Microscopic Examination of Liver.—Very slight ascending angiocholitis with moderate biliary sclerosis of the large trunks. No embryonic proliferation. Capillary inflammation more marked than in all the previous livers; congestion of medium intensity; no hemorrhages. Cellular alterations of the same nature as in the other experiments with bacillus coli and coli-toxin.

Microscopic Examination of the Kidneys.—Cloudy swelling of the epithelium. Very pronounced capillary inflammation.

Microscopic Examination of the Lungs.—The alveoli are filled with blood. There is a very intense capillary inflammation. The walls of the extra-lobular branches of the pulmonary artery are markedly thickened.

EXPERIMENT XXXVIII.

COLI-TOXIN AND ALCOHOL.—*Duration: one month.*—Rabbit of 1565 grams, beginning May 27, 1893, daily takes half a cubic centimetre of a one-month culture of coli-toxin with 10 c.c. of 95 per cent. alcohol. The animal was found dead at 3 P.M. June 26th. It weighed 1300 grams.

Autopsy.

Liver weighs 43 grams, light brown. The mucous membrane of the *stomach* is sown with little punctiform hemorrhages which give to it a general reddish-brown appearance. The *intestine* appears normal. The *lungs* are congested; there is a hemorrhagic centre at the base of the left lung.

Microscopic Examination of the Liver.—Ascending angiocholitis with moderate sclerosis of the large trunks. Embryonic proliferation of the medium and small portal spaces, rings of sclerosis on some, as plainly venous as biliary. Cellular alterations similar to those of the preceding livers. No fatty degeneration. Capillaries moderately distended with blood, especially about the central vein.

Experiment xxxix.

Coli-Toxin and Alcohol.—*Duration: two months, eight days.*—Rabbit of 1930 grams, beginning on June 28, 1893, takes daily 2 c.c. of a one-month culture of coli-toxin and 20 c.c. of 95 per cent. alcohol. July 11th, he weighs 1625 grams. The toxin being exhausted, until the end he took nothing but alcohol. Nevertheless he continued to grow thin and died September 5th, weighing 1020 grams.

Autopsy.

Liver weighs 20 grams; it is the color of the lees of wine. *Stomach:* some ecchymoses on the mucous membrane.

Microscopic Examination of the Liver.—Absolutely comparable to that of the preceding liver. No fatty degeneration.

Experiment xl.

Coli-Toxin and Alcohol.—*Duration: eight days.*—Rabbit of 1645 grams daily takes, commencing May 25, 1893, half a cubic centimetre of a one-month culture of coli-toxin and 10 c.c. of alcohol. On June 1st, he weighs 1330 grams. He became cold without having any convulsive action. At 5.30 P.M., the rectal temperature was 35°.4 C.; at 8 P.M., 34°.1 C. Died at 8.45 P.M.

Autopsy.

Liver weighs 45 grams; dark colored, congested. *Stomach* and *intestine:* mucous membrane simply colored a dark red without ecchymoses. *Kidneys* appear normal to the naked eye. The bladder is very full of a slightly muddy urine, somewhat colored, which contains albumin but no sugar or urobilin.

Microscopic Examination of the Liver.—Similar to the preceding livers; but the cellular destruction is more general and more complete; the nuclei themselves remain extremely pale with various reagents. No fatty degeneration.

HUMAN FÆCES.

As a corollary, as a synthesis rather of the action of various noxious substances contained in the intestine, it was deemed advisable to study the effect of the absorption of fæcal matters. As we could not think of giving them to the animals in kind, an extract was prepared which we have succeeded in administering to the rabbits by mixing it with some bran.

A fæcal mass from a man in perfect health was thoroughly desiccated, pulverized, then treated with ether to remove any fatty matters which it might contain, and the residue exhausted with alcohol. This alcoholic residue was afterwards reduced to an extract by evaporation. The entire operation was repeated whenever the supply of extract was exhausted.

EXPERIMENT XLI.

EXTRACT OF FÆCES.—*Duration: one month, two days.*—Rabbit of 1680 grams, commencing June 13, 1893, daily ingests 2 grams of extract of fæces. He was found dead on the morning of July 15th, weighing only 965 grams.

Autopsy.

Liver weighs 23 grams. The color is all but normal. It is hard upon section and presents on the surface some little white star-shaped tracts. There is no alteration of the *stomach* or *intestine*. The *kidneys* and *spleen* are very small.

Microscopic Examination of the Liver.—No ascending angiocholitis. The medium-sized and small portal spaces are the seat of an embryonic connective-tissue hyperplasia. The capillaries are gorged with blood. Numerous intra-parenchymatous hemorrhages. Very profound cellular lesions comparable to those of the livers of bacillus coli or coli-toxin.

Microscopic Examination of the Kidneys.—Cloudy swelling of the epithelium. Commencing capillary inflammation.

Microscopic Examination of Lungs.—Intense congestion; there are no hemorrhages, but the alveoli are full of red globules.

EXPERIMENT XLII.

EXTRACT OF FÆCES.—*Duration: twelve days.*—Rabbit of 1680 grams was subjected to the same régime as the preceding

one, commencing July 19, 1893. He died August 1st, weighing 1460 grams.

Autopsy.

Liver weighs 59 grams. The *lungs* are congested. Nothing abnormal in the other organs.

Microscopical Examination of Liver, Kidneys, and Lungs.—In all points comparable to the preceding.

EXPERIMENT XLIII.

EXTRACT OF FÆCES.—*Duration: one month, twenty-eight days.*—Rabbit of 1970 grams ingested 2 grams of fæcal extract daily, beginning August 5, 1893. He died on October 3d, at 5 P.M., weighing 1200 grams.

Autopsy.

Liver weighs 30 grams; it is a reddish-brown color. *Lungs* very much congested. Nothing particular in the other organs.

Microscopic Examination of Liver, Kidneys, and Lungs.—Entirely similar to the preceding.

RECAPITULATION.

If we will refer to Experiment I, we will see that *butyric acid,* of itself alone, is capable of determining lesions in the liver which experimentally realize the *atrophic cirrhosis of Lænnec. Lactic* and *valerianic acids* have given less complete results, less absolute, but entirely of the same order; *acetic acid* has likewise produced a very pronounced cirrhosis, and it is, of these four agents, that one which I would be led to consider as endowed with the greatest sclerogenic power. In fact, whilst we have been able to administer butyric acid for the space of three months, acetic acid, moreover very much disliked by the animals, has produced, in thirty-six days, lesions almost as extensive as butyric acid. It also destroys the animals more rapidly than the latter substance, as its action upon the hepatic cell is much more toxic.

Of all the poisons of the alimentary canal, acetic acid is the most dangerous, since it is to a high degree both irritating and degenerating. The cirrhosis produced is both venous and biliary.

As I have previously said, let a noxious substance, irritant to the vessels, daily arrive at the liver in very small quantity: under such circumstances, the cell has ample time and force to

annihilate it as it arrives, the injurious action being confined to the blood-vessels, perhaps to the capillaries alone.

But let the toxic substance be transported there in larger quantity, it surprises, in some sort, the cell impotent to transform this poison, which affects it either functionally, or organically by producing its degeneration. The poison then passes freely into the circulation and also into the biliary passages, there inducing *descending* angiocholitis, the small vessels being first affected.

This is the cause of the canalicular neo-formation, which we find in infectious livers especially, and which may also take place in toxic livers. Such is the line of union of the poisons and the toxins, of the chemical and the living agent, their ultimate action being analogous, as many cases daily demonstrate, and which we see in so evident a manner, for the liver itself, in the grave icterus which phosphorus and the various microbes, specific or not, encountered in this disease, may produce through the destruction of the hepatic cells.

The fatty acids proper have not induced the least connective-tissue proliferation. I have above remarked that several of the rabbits died of tuberculosis. These were more especially the animals which took the fatty acids: butyric, valerianic, and lactic acids, but with no alcohol. In addition, these rabbits were less vigorous than the others, which were expressly selected, the finest animals being reserved for the ingestion of various substances with alcohol.

I have believed it to be unnecessary to report these cases here. I have, however, preserved one of them (Exp. XVI.), which seems to me to show quite clearly that (which the other experiments cause me, if not to admit, at least to suspect) the constant or frequent presence of fatty acids or acids of fermentation in the alimentary canal greatly favors a possible tuberculization.

The rabbit of Exp. XVI. lived for eight months and twenty-six days after it began to take the fatty acids, and, save a transient loss of weight a few days after the commencement of this unusual diet, and a second diminution, likewise temporary, after an increase of the amount of fatty acids administered, the animal remained vigorous and of fine appearance. Notwithstanding its vigor and its more favorable conditions of nourishment and hygiene (save liberty), it became tuberculous at the end of eight months, and death took place a month afterwards. The other rabbits were less resistant and their history is less interesting. Moreover, it is

to be remarked that most of the tubercles were found in the lungs; there were some also in the liver, but a much smaller number; which signifies that, notwithstanding the unhealthy condition of the hepatic cells, certainly anterior to the beginning of the tuberculization, the liver was not the principal point of attack of the tuberculosis. Must we conclude from this that gastro-intestinal disturbances predispose to tuberculosis; that the initial gastric syndrome of the tuberculous, investigated by M. Marfan, is not the effect of an incipient tuberculosis, but a pre-tuberculous condition determining the invasion of the organism by the bacillus of Koch?

This would be exaggerating things very much and, it seems to me that we may be scrupulously exact, if we recognize the fact that dyspeptic conditions favor tuberculization with predisposed persons, with those individuals whose primitive defect is manifested by the congenital malformations or the arrests of development which we encounter with the tuberculous: narrowness of chest and thoracic malformations, osseous system imperfectly developed, lack of cardiac and arterial development.

As to the gastric syndrome of M. Marfan, it may be only an exaggeration, under the influence of the commencing tuberculosis, of the anterior dyspeptic troubles, which have probably favored the germination of the tuberculosis in the prepared soil. We have here again the vicious circle which we encounter whenever it is a question of studying the reciprocal relations of two functional disturbances; and always we ask ourselves the same question, sometimes easy to answer, sometimes unanswerable: in which organ did the disturbance commence? It is the history of the influence of gastro-intestinal diseases upon the liver and of diseases of the liver upon the condition of the alimentary canal. We may encounter some cases in which it will be a very difficult matter to determine the responsibility of the liver or of the intestine. With cirrhosis itself, the common cirrhosis of drunkards, we have seen that the gastric disturbances, which form a portion of the minor symptoms of Hanot, can only be an exaggeration, under the influence of the commencing hepatic affection, of anterior dyspeptic troubles provoked by alcoholic drinks, and which have favored, if not determined, the sclerosis and the degeneration of the liver.

To return to tuberculosis, it is certain that, this disease once established and the digestive disturbances confirmed, the hepatic

gland has to suffer greatly from the products of defective digestion, as much as from the presence in the organism of the various microbian toxins (toxin of tuberculosis and the toxins of the secondary microbes) which are there elaborated.

In the chapter on pathological anatomy, we have seen how the dyspeptic cirrhosis, which I have described, has some analogies, from the point of view of the location of the sclerosis, with that form of the liver of the tuberculous called: *fatty hypertrophic cirrhosis.*

Acetone quickly destroyed three rabbits; two in seven days with a dose of 10 c.c., one in sixteen days with a dose of 4 c.c. The lesion invariably present was an epithelial nephritis, which Ebstein and Straus have described in connection with diabetes, a sort of necrotic coagulation manifesting itself during life by a marked albuminuria. It is this *acetonic nephritis* which Albertoni and Pisenti [1] have experimentally produced with dogs and rabbits.

In my preparations I have not met with the hyaline degeneration noticed with diabetics by Armanni and Ehrlich. As to the *liver*, we have been able to see that, with the two animals which took 10 c.c. of acetone and which were undoubtedly destroyed by nephritis, the lesions solely affected the cells. These same lesions were at their maximum with the rabbit which lived sixteen days, taking 4 c.c. of acetone daily, but besides, there was a certain degree, very appreciable in some portal spaces, of embryonic infiltration, as much venous as biliary.

By diminishing the daily amount of acetone, after repeated trials, we might succeed in so disposing the cell as to make possible the production of a cirrhosis. From thence to affirming that diabetic cirrhosis may recognize such an origin, is too great a distance for me to leap, at least just at present.

The examination of the organs of the rabbits poisoned by acetone has enabled me to see some other details which I have purposely kept in the background, waiting an opportunity to make a more careful investigation of the subject.

Aldehyde has proven itself to be a substance with a feeble sclerosing action, but as a poison of the hepatic cell, we would be tempted to connect it with alcohol, only the latter substance has a fat-producing action, whilst aldehyde induces a granular degeneration.

[1] *Cf.* Pisenti e Acri, "Rene Diabetico," *Acc. med. chir. d. Perugia*, 1890.

Oxalic acid induces gastro-intestinal inflammation and consequently favors the production of ascending angiocholitis. But eventually it appears to have an irritative action upon the portal vessels, as is proven by a certain degree of sclerosis of the small spaces. On the other hand, it destroys the hepatic cells, which die in a condition of granular degeneration. It also rapidly produces parenchymatous nephritis, so that, in order to produce a sclerosis of any importance, it would be necessary to administer very small doses of the acid and keep up its administration for a very long time.

Budd and Virchow have deservedly incriminated *pepper* as a cause of cirrhosis. With the rabbit, in a month's time it produced a decided porto-biliary sclerosis with tendency to penetration of the lobules, and it also induced a fatty degeneration of the hepatic cells. It likewise acts upon the kidneys, producing a necrosis of the epithelium and a capillary inflammation with embryonic connective-tissue proliferation.

The action, common to *the living cultures of Bacterium coli* and to the various *coli-toxins* employed in the experiments, may be summarized in the following terms: production, all but constant, of an ascending angiocholitis with rapid and extensive sclerosis of the large portal spaces;—manifest irritative action upon the portal vessels of small and medium calibre, which sometimes present some endoarteritis, sometimes a limited sclerosis, almost always an embryonic infiltration more or less discrete; the supra-hepatic veins themselves may participate in this process; the result of this irritative action is again found in the biliary canals of the same spaces;—tendency to capillary inflammation and, according to the amount administered and the suddenness rather than the duration of the action, an intense congestion and hemorrhages not only in the liver, but also in the kidneys and especially in the lungs;—granular necrosis of the hepatic cells with vesicular condition of the nuclei when the action has been profound and rapid, or simply granular degeneration of the protoplasm with nuclear irritation if the action has been less sudden and more prolonged;—lastly, in the cases in which the toxi-infection has been rapid and severe, production of ecchymoses upon the gastro-intestinal mucous membrane.

The ascending angiocholitis has its *raison d'être* in the greater virulence of the bacillus coli introduced, and, if we are experimenting with coli-toxin, in the increase of virulence which its

arrival in the alimentary canal produces in the micro-organisms which normally inhabit it; in both cases, the greater vitality of the microbe, added to a weakening of the hepatic function under the influence of the poisons absorbed, is the cause of the invasion of the choledochus, so arranged, with the rabbit especially, as to give an asylum to the normal or abnormal guests of the intestine.

The capillary inflammation is much more pronounced and is generalized in the other organs if, instead of causing the animals to ingest the culture and especially the toxin, we inject it into the veins. We may convince ourselves of this fact by referring to Exp. XXXVII. Some other experiments which I have not here reported, in which venous injection was employed, have given the same results. So if, for one reason or another, small amount or greater resistance, the hepatic cell succeeds in escaping the necrosing action of the coli-toxin, the ultimate effect of this microbian poison is to produce not only hepatic cirrhosis, but, in addition, sclerosis of the whole vascular system. Extract of fæces has given results comparable to those of coli-toxin.

I now come to the rôle which alcohol has played in these experiments. With the preconceived idea that it would add its noxious action to that of the various substances ingested, I purposely selected the fattest and most vigorous animals, in order that the experiment might last as long as possible. It has happened that, not only all the animals, which took alcohol in addition to the poisonous chemicals, have lived a very much longer time than those not taking it, a year and more, but likewise the sclerosis was infinitely less, sometimes entirely absent.

The cellular destruction, caused by the toxic agent administered with the alcohol, was not produced so rapidly, and in all the cases, the dominant lesion has been the steatosis. It would seem as if the alcohol had neutralized, I know not how, the poison administered, as if it had strengthened the organism and the liver itself, as if it had reserved for itself the right of slowly destroying the hepatic cell, and in its own way. It is very difficult to state precisely the determinism of such a fact. The cause of it is not to be found in the greater individual resistance of the selected animals.

All the organic acids are but slightly soluble in alcohol, it is true; some only dissolve in boiling alcohol itself. Perhaps this is the reason for their direct passage into the fæces and of their arrival at the liver in very small quantity. Possibly also, the

alcohol, coagulating the stomachal and intestinal mucus, or the albuminoid substances of the ingesta, has been included in the coagulum and expelled with the fæcal matters.

I hasten to add that nothing similar happened with the animals which ingested coli-toxin and alcohol at the same time. The latter substance apparently had no effect, undoubtedly on account of the great noxiousness of the substance with which it was associated. A very valuable lesson is to be derived from these experiments; it is that *alcohol addresses itself especially to the hepatic cell, for which it is essentially steatogenic.* This action is only slowly produced and at the expiration of a long period. This corroborates the conclusions of previous experimenters, namely: first, that moderate amounts of alcohol, far from having an injurious action upon the organism, and in particular upon the liver, on the contrary aid in the preservation of the general health, and permit the opposing of a greater resistance to the different agents of intoxication or infection. Second, that large amounts of alcohol, solely taking the liver into consideration, address their toxic action almost exclusively to the hepatic cells, of which they eventually provoke a fatty degeneration.

Alcohol is, then, toxic but not irritant to the liver; it is so to a high degree, so far as the mucous membrane of the stomach is concerned. The gastritis of drunkards is a thing so common (whatever may be its form, hyperpeptic, mucous, ulcerative, or hemorrhagic), that it is perhaps to it and not to the alcohol that it would be proper to attribute a large number of the so-called alcoholic cirrhoses; the chronic gastritis terminating in dilatation of the stomach and alimentary stasis, that is, in abnormal fermentations. And moreover, is it principally alcohol which the so-called alcoholic (*ethyliques*) drunkards drink?

M. Lancereaux has rightly remarked that wine drinkers are especially subject to cirrhosis. Now, in wine there is only ten per cent. of alcohol, and, in addition, it contains small amounts of other substances with which we do not concern ourselves: coloring matters, several kinds of ethers, aldehydes, acetones, and acetic acid. On the other hand, once in the stomach, wine undergoes the acetic fermentation. As to drinkers of alcohol in the form of brandy, raw spirits, absinthe, liqueurs, etc., it is generally amylic alcohol which they are in the habit of drinking and with it a large quantity of essences, the toxicity of which is no longer questionable, and from which the stomach has more to suffer than the

liver. We know that the alcohol drunk by the laborers of the north, at Rouen in particular, is a heterogeneous product and horribly impure, even containing *sulphuric acid.*

Very many other considerations would in addition plead against the alcoholic origin, at least direct, of cirrhosis. But I have promised not to defend the case of alcohol, which in truth is not the design of this work. It is only as a corollary of my experiments that I have ventured the preceding reflections. If alcohol must disappear from the scene or pass to a subordinate position in the etiology of the cirrhoses, may it die a happy death.

We must not fail to observe that the substances employed in our experiments have produced in the liver of the animals, not a diffused hypertrophic cirrhosis with mono-cellular tendency, as we might be led to expect after reading the first two parts of this thesis, but an atrophic cirrhosis comparable to that of Laennec. I cannot help this, and I content myself with simply recording the cases and the facts. Certain conditions which I do not care to take under consideration at the present time, as I do not wish to enter into the domain of pure hypothesis, perhaps prescribe the location of the connective-tissue process.

Conclusions.

Of all the preceding portions of this work, the following propositions should be retained.

First, alcohol is not everything in the etiology of cirrhosis of the liver. Its pathogenic rôle demands a searching inquiry, which a long term of years can alone bring to a successful termination. In fact, it is indispensable that the condition of the alimentary canal should be carefully investigated with those suffering from cirrhosis, and an attempt made to ascertain if, with them, fermentations of gastrio-intestinal origin do not give rise to the production of substances which are endowed with properties both irritating and toxic to the liver.

Second, entirely independent of the alcoholic habit, we frequently encounter a pathological condition of the liver with dyspeptics, which is manifested by increase of the size of this organ; it is the *dyspeptic liver.*

Third, this increase of size is temporary or permanent. Temporary, with frequent returns, it constitutes the *hepatic congestion* noticed for a long time by various authors, and especially by M. Bouchard. Permanent, it is *dyspeptic cirrhosis.*

Fourth, this *dyspeptic cirrhosis*, described for the first time in this work, is manifested: *clinically*, by an enlarged liver, smooth, *remarkably hard* (like wood), without increase in size of the spleen, without icterus, ascites, or development of the collateral abdominal circulation; *histologically*, by a diffused generalized cirrhosis, inter- and intra-lobular, with mono-cellular tendency, with relative integrity of the hepatic cells.

Fifth, the duration of such an affection is very long, ten years and more, the size of the liver remaining almost the same. The termination may take place, as in the atrophic cirrhosis of Laennec, by exaggeration of the mechanical interference and production of ascites and enlarged abdominal veins, and also by terminal infection. The prognosis is then, as always, connected with the condition of the hepatic cells.

Sixth, among the toxic substances which are elaborated in the alimentary canal, we must consider the acids of fermentation as possessing a marked sclerogenic action: butyric, lactic, valerianic, and especially acetic acid.

As to coli-toxin, it is probable that it also has a sclerosing action upon the liver, unless it reaches this organ in an amount sufficient to rapidly destroy the hepatic cells.

Seventh, we must also take into consideration the predisposition most frequently created by the gouty diathesis (*arthritisme*, Hanot).

Eighth, dyspeptic cirrhosis can only be confounded with cancer of the liver, from which it is distinguished by its very long duration; or with a large lithiasic liver (*lithiasique*), which is most frequently accompanied by icterus; or with an enlarged alcoholic liver, with which we will ordinarily find a large spleen and very soon ascites and enlargement of the subcutaneous abdominal veins.

Ninth, the treatment should be especially addressed to the digestive functions. Intestinal antisepsis will be of very great assistance, and will give very satisfactory results, especially in the congestive forms. Calomel, in the dose of one centigram, may be successfully prescribed.

THE END.

Standard Medical Publications.

BERNHEIM. Suggestive Therapeutics. A Treatise on the Nature and Uses of Hypnotism. By H. BERNHEIM, M.D., Professor in the Faculty of Medicine at Nancy. Translated from the second and revised French edition, by CHRISTIAN A. HERTER, M.D., of New York. 8°, cloth $3 50

"Nowhere else will the reader find so complete an account of the manipulation of hypnotic suggestions used to cure diseases; and the preferences of the author do not lead him to lengths which are not fully to be accounted for by his natural enthusiasm and the seductive nature of his subject."—*Medical and Surgical Reporter.*

"The book is both thoughtful and practical, and claims thorough reading and earnest consideration. It contains truths without some grasp of which no physician is fit for his charge."—*N. E. Medical Gazette.*

CUTLER. Manual of Differential Medical Diagnosis. By CONDICT W. CUTLER, M.S., M.D. 16°, cloth $1 25

"This manual has decided merit, and will commend itself to every one engaged in the study of medicine. . . . The author displays rare skill and judgment in contrasting disease. His differentiation is clear, but not too sharply drawn, and displays extensive labor and research as well as practical knowledge."—*N. Y. Medical Journal.*

DAWBARN. An Aid to Materia Medica. By ROBT. H. DAWBARN, M.D. Revised and adapted to the U. S. Pharmacopœia of 1890, by WOOLSEY HOPKINS, M.D. 16°, cloth $1 25

"Such a work as this is especially important to students because examiners require much that the practitioner soon lays aside. . . . We are sure that no intelligent practitioner can afford to neglect to place this little book upon his working-table and always keep it there."—*American Lancet.*

"This book will be found extremely interesting."—*Journal Am. Med. Ass'n.*

HERSCHELL. Indigestion. An Introduction to the Study of the Diseases of the Stomach. By GEORGE HERSCHELL, M.D., London. Second edition, revised and enlarged, 12°, cloth $2 00

HERTER. The Diagnosis of Diseases of the Nervous System. A Manual for Students and Practitioners. By CHRISTIAN A. HERTER, M.D., Physician to the Class of Nervous Diseases, Presbyterian Hospital Dispensary, New York City. Illustrated, 12°, cloth . . $3 00

"We do not hesitate in saying that it is one of the best books we have seen. It shows that it is the product of a well-ordered mind."—*Medical Journal.*

KRAFFT-EBING. An Experimental Study in the Domain of Hypnotism. By R. VON KRAFFT-EBING, Professor of Psychiatry and Nervous Disease in the University of Graz, Austria. Translated by CHAS. G. CHADDOCK, M.D., Assistant Physician, Northern Michigan Asylum. 8°, cloth $1 25

"This little monograph by one of the greatest alienists in Germany has already become classical; and amid the mass of rubbish written on hypnotism, it stands as one of the few exhaustive scientific studies. It is with pleasure, therefore, that we greet the work in a form accessible to the English reader."—*Boston Medical and Surgical Journal.*

LETCHWORTH. The Insane in Foreign Countries. Notes of an Examination of European Methods of Caring for the Insane. By Hon. WM. P. LETCHWORTH, President of the New York Board of Charities. 8°, with many illustrations $3 00

"Every person interested in the welfare of the insane poor, and the provision made for their protection and support in different countries, will find this a most interesting and valuable volume; and equally so whether such person be a physician or not."—*Journal of the American Medical Association.*

MEDICAL REGISTER (The), of New York, New Jersey, and Connecticut. Published Annually under the supervision of the New York Medico-Historical Society. Edited by JOHN SHRADY, M.D. 12°, cloth $2 50

MORRIS. How We Treat Wounds To-Day. A Treatise on the Subject of Antiseptic Surgery which can be understood by beginners. By ROBERT T. MORRIS, M.D. 16°, cloth $1 00

——— Lectures on Appendicitis, and Notes on other Subjects. By ROBERT T. MORRIS, M.D. With numerous illustrations. 8°, $2 00

PUBLISHED BY G. P. PUTNAM'S SONS, 27 West 23d St., New York City.

Standard Medical Publications.

MACFARLANE. A Clinical Manual. A Guide to the Practical Examination of the Excretions, Secretions, and the Blood; for the use of Physicians and Students. By ANDREW MACFARLANE, A.B., M.D., Instructor in Neurology in the Albany Medical College, Physician to St. Peter's Hospital Out-Patient Department, and Physician to Albany's Hospital for Incurables. 12°, cloth $1 25

"The author has condensed and arranged the matter in such a manner that a large number of practical hints and an abundance of valuable knowledge is easily in reach of the student and busy practitioner."—*Med. Bulletin.*

NURSING (A MANUAL OF). Prepared for the Training School for Nurses attached to Bellevue Hospital. By MARY PUTNAM JACOBI, M.D., and VICTORIA WHITE, M.D. 16°, boards . . . 75

NUTTALL. Hygienic Measures in Relation to Infectious Diseases. Information as to the Cause and Mode of Spreading of Certain Diseases; the Preventive Measures that should be Resorted to: Isolation, Disinfection, etc. By GEORGE F. H. NUTTALL, M.D., Ph.D. (Gottingen). 16° cloth 75

PARKER. Cancer: Its Nature and Etiology. With Tables of 397 Illustrated Cases. By WILLARD PARKER, M.D. 8°, cloth . $1 50

"Will prove of value to all who are interested in cancer."—*National Druggist.*

SEIFERT AND MÜLLER. Manual of Clinical Diagnosis. New (fifth) Edition. With 60 illustrations and lithographic frontispiece printed in colors. By Dr. OTTO SEIFERT, Privatdocent in Wurzburg, and Dr. FRIEDRICH MÜLLER, Assistent der II. med. Klinik in Berlin. Translated with the author's permission, from the fifth revised and enlarged edition, by WILLIAM BUCKINGHAM CANFIELD, A.M., M.D. 8°, cloth $1 50

"Admirably adapted to the practical need of the physician and surgeon, and we would most heartily commend it."—*Buffalo Medical and Surgical Journal.*

SCHIMMELBUSCH. A Guide to the Aseptic Treatment of Wounds. By Dr. C. SCHIMMELBUSCH. Translated from the German by F. J. THORNBURY, M.D., Lecturer on Bacteriology, University of Buffalo, N. Y.; Supervising Microscopist in the Bureau of Animal Industry, U. S. Department of Agriculture, Cincinnati, Ohio, etc. With 41 illustrations. 12°, cloth $2 00

TUCKEY. Psycho-Therapeutics; or Treatment by Hypnotism and Suggestion. By C. LLOYD TUCKEY, Member of the Medico-Psychological Association. Membre Fondateur de la Société d'Hypnologie. Third edition. Revised and enlarged. 8°, cloth . . $2 00

UFFLEMANN. Manual of the Domestic Hygiene of the Child. For the use of Students, Physicians, Sanitary Officials, Teachers, and Mothers. By JULIUS UFFELMANN, M.D., Professor of Internal Medicine at the University of Rostock. Translated, with the author's permission, by HARRIET RANSOM MILINOWSKI. Edited by MARY PUTNAM-JACOBI, M.D. 8°, cloth $1 75

USHER. Alcoholism and Its Treatment. By J. E. USHER, M.D., London. 12°, cloth $1 25

PUBLISHED BY G. P. PUTNAM'S SONS, 27 West 23d St., New York City.